US 20190202893A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2019/0202893 A1**

Falkner et al. (43) **Pub. Date: Jul. 4, 2019**

(54) **VIRAL VECTORS ENCODING RECOMBINANT FVIII VARIANTS WITH INCREASED EXPRESSION FOR GENE THERAPY OF HEMOPHILIA A**

(71) Applicants: **Baxalta Incorporated**, Bannockburn, IL (US); **Baxalta GmbH**, Zug (CH)

(72) Inventors: **Falko-Günter Falkner**, Orth (AT); **Franziska Horling**, Gaenserndorf (AT); **Johannes Lengler**, Vienna (AT); **Hanspeter Rottensteiner**, Vienna (AT); **Friedrich Scheiflinger**, Vienna (AT)

(21) Appl. No.: **16/211,201**

(22) Filed: **Dec. 5, 2018**

Related U.S. Application Data

(63) Continuation of application No. 15/349,930, filed on Nov. 11, 2016, now Pat. No. 10,189,888.

(60) Provisional application No. 62/255,317, filed on Nov. 13, 2015.

Publication Classification

(51) **Int. Cl.**

C07K 14/755	(2006.01)
A61K 48/00	(2006.01)
C12N 15/86	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 14/755*** (2013.01); ***A61K 48/0066*** (2013.01); ***A61K 48/0058*** (2013.01); *C12N 2800/22* (2013.01); ***C12N 15/86*** (2013.01); *C12N 2840/007* (2013.01); *C12N 2750/14143* (2013.01); ***A61K 48/0008*** (2013.01)

(57) **ABSTRACT**

The present disclosure provides, among other aspects, codon-altered polynucleotides encoding Factor VIII variants for expression in mammalian cells. In some embodiments, the disclosure also provides mammalian gene therapy vectors and methods for treating hemophilia A.

Specification includes a Sequence Listing.

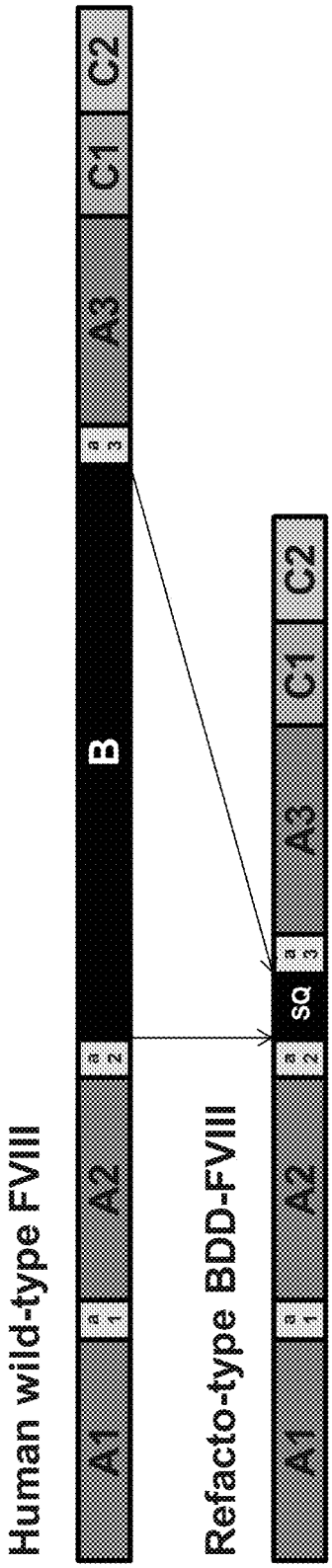

Human wild-type FVIII
A1
a1
A2
a2
B
a3
A3
C1
C2
Refacto-type BDD-FVIII
A1
a1
A2
a2
sq
a3
A3
C1
C2

Figure 1

CS04-FL-NA

```
atgcagattgagctgagcacctgcttcttcctgtgcctgctgaggttctgcttctctgccaccagga
gatactacctgggggctgtggagctttcttgggactacatgcagtctgacctgggggagctgcctgt
ggatgccaggttcccacccagagtgcccaaatccttcccattcaacacctctgtggtctacaagaag
accctctttgtggagttcactgaccacctgttcaacattgccaaacccaggccaccctggatgggac
tcctgggacccaccattcaggctgaggtgtatgacactgtggtcatcaccctcaagaacatggcctc
ccaccctgtgagcctgcatgctgtgggggtcagctactggaaggcctctgagggggctgagtatgat
gaccagacctcccagagggagaaggaggatgacaaagtgttccctgggggcagccacacctatgtgt
ggcaggtcctcaaggagaatggccccatggcctctgacccactctgcctgacctactcctacctttc
tcatgtggacctggtcaaggacctcaactctggactgattggggccctgctggtgtgcagggagggc
tccctggccaaagagaagacccagaccctgcacaagttcattctcctgtttgctgtctttgatgagg
gcaagagctggcactctgaaaccaagaactccctgatgcaggacagggatgctgcctctgccagggc
ctggcccaagatgcacactgtgaatggctatgtgaacaggagcctgcctggactcattggctgccac
aggaaatctgtctactggcatgtgattggcatggggacaacccctgaggtgcactccatttttcctgg
agggccacaccttcctggtcaggaaccacagacaggccagcctggagatcagccccatcaccttcct
cactgcccagaccctgctgatggacctcggacagttcctgctgttctgccacatcagctcccaccag
catgatggcatggaggcctatgtcaaggtggacagctgccctgaggagccacagctcaggatgaaga
acaatgaggaggctgaggactatgatgatgacctgactgactctgagatggatgtggtccgctttga
tgatgacaacagcccatccttcattcagatcaggtctgtggccaagaaacaccccaagacctgggtg
cactacattgctgctgaggaggaggactgggactatgccccactggtcctggcccctgatgacagga
gctacaagagccagtacctcaacaatggcccacagaggattggacgcaagtacaagaaagtcaggtt
catggcctacactgatgaaaccttcaagaccagggaggccattcagcatgagtctggcatcctgggc
ccactcctgtatggggaggtggggacaccctgctcatcatcttcaagaaccaggcctccaggccct
acaacatctacccacatggcatcactgatgtcaggcccctgtacagccgcaggctgccaaaggggct
gaaacacctcaaggacttccccattctgcctggggagatcttcaagtacaagtggactgtcactgtg
gaggatggaccaaccaaatctgaccccaggtgcctcaccagatactactccagctttgtgaacatgg
agagggacctggcctctggcctgattggcccactgctcatctgctacaaggagtctgtggaccagag
gggaaaccagatcatgtctgacaagaggaatgtgattctgttctctgtctttgatgagaacaggagc
tggtacctgactgagaacattcagcgcttcctgcccaaccctgctggggtgcagctggaggaccctg
agttccaggccagcaacatcatgcactccatcaatggctatgtgtttgacagcctccagctttctgt
ctgcctgcatgaggtggcctactggtacattctttctattggggcccagactgacttcctttctgtc
ttcttctctggctacaccttcaaacacaagatggtgtatgaggacaccctgaccctcttcccattct
ctggggagactgtgttcatgagcatggagaaccctggcctgtggattctgggatgccacaactctga
cttccgcaacaggggcatgactgccctgctcaaagtctcctcctgtgacaagaacactggggactac
tatgaggacagctatgaggacatctctgcctacctgctcagcaagaacaatgccattgagcccagga
gcttcagccagaatccacctgtcctgaaacgccaccagagggagatcaccaggaccaccctccagtc
tgaccaggaggagattgactatgatgacaccatttctgtggagatgaagaaagaggactttgacatc
tatgacgaggacgagaaccagagcccaaggagcttccagaagaagaccaggcactacttcattgctg
ctgtggagcgcctgtgggactatggcatgagctccagccccatgtcctcaggaacagggcccagtc
tggctctgtgccacagttcaagaaagtggtcttccaaagagttcactgatggcagcttcacccagccc
ctgtacagaggggagctgaatgagcacctgggactcctgggcccatacatcagggctgaggtggagg
acaacatcatggtgaccttccgcaaccaggcctccaggccctacagcttctacagctccctcatcag
ctatgagGaggaccagaggcaggggggctgagccacgcaagaactttgtgaaacccaatgaaaccaag
acctacttctggaaagtccagcaccacatggcccccaccaaggatgagtttgactgcaaggcctggg
```

(Continued)

Figure 2A

cctacttctctgatgtggacctggagaaggatgtgcactctggcctgattggcccactcctggtctg
ccacaccaacaccctgaaccctgcccatggaaggcaagtgactgtgcaggagtttgccctcttcttc
accatctttgatgaaaccaagagctggtacttcactgagaacatggagcgcaactgcagggccccat
gcaacattcagatggaggaccccaccttcaaagagaactaccgcttccatgccatcaatggctacat
catggacaccctgcctgggcttgtcatggcccaggaccagaggatcaggtggtacctgctttctatg
ggctccaatgagaacattcactccatccacttctctgggcatgtcttcactgtgcgcaagaaggagg
agtacaagatggccctgtacaacctctaccctggggtctttgagactgtggagatgctgccctccaa
agctggcatctggagggtggagtgcctcattggggagcacctgcatgctggcatgagcaccctgttc
ctggtctacagcaacaagtgccagacccccctgggaatggcctctggccacatcagggacttccaga
tcactgcctctggccagtatggccagtgggccccaagctggccaggctccactactctggatccat
caatgcctggagcaccaaggagccattcagctggatcaaagtggacctgctggcccccatgatcatc
catggcatcaagacccaggggccaggcagaagttctccagcctgtacatcagccagttcatcatca
tgtacagcctggatggcaagaaatggcagacctacagaggcaactccactggaacactcatggtctt
ctttggcaatgtggacagctctggcatcaagcacaacatcttcaacccccccaatcatcgccagatac
atcaggctgcaccccacccactacagcatccgcagcaccctcaggatggagctgatgggctgtgacc
tgaactcctgcagcatgcccctgggcatggagagcaaggccatttctgatgcccagatcactgcctc
cagctacttcaccaacatgtttgccacctggagcccaagcaaggccaggctgcacctccagggaagg
agcaatgcctggaggccccaggtcaacaacccaaaggagtggctgcaggtggacttccagaagacca
tgaaggtcactggggtgaccacccaggggtcaagagcctgctcaccagcatgtatgtgaaggagtt
cctgatcagctccagccaggatggccaccagtggaccctcttcttccagaatggcaaggtcaaggtg
ttccagggcaaccaggacagcttcacCcctgtggtgaacagcctggacccccccctcctgaccagat
acctgaggattcacccccagagctgggtccaccagattgccctgaggatggaggtcctgggatgtga
ggcccaggacctgtactga (SEQ ID NO:1)

Figure 2B

CS04-FL-AA

MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDAR'FPPRVPKSFPFNTSVVYK
KTLFVEFTDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEY
DDQTSQREKEDDKVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCRE
GSLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGC
HRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLFCHISSH
QHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKKHPKTW
VHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQHESGIL
GPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIFKYKWTVT
VEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVILFSVFDENR
SWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILSIGAQTDFLS
VFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGD
YYEDSYEDISAYLLSKNNAIEPRSFSQNPPVLKRHQREITRTTLQSDQEEIDYDDTISVEMKKEDFD
IYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSPHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQ
PLYRGELNEHLGLLGPYIRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNET
KTYFWKVQHHMAPTKDEFDCKAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALF
FTIFDETKSWYFTENMERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLS
MGSNENIHSIHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTL
FLVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDLLAPMI
IHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNIFNPPIIAR
YIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSPSKARLHLQG
RSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSSQDGHQWTLFFQNGKVK
VFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY (SEQ ID NO:2)

Figure 3

CS04-HC-NA

gcc
accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg
ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac
acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt
gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat
gacactgtgg tcatcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg
ggggtcagct actggaaggc ctctgagggg gctgagtatg atgaccagac ctcccagagg
gagaaggagg atgacaaagt gttccctggg ggcagccaca cctatgtgtg gcaggtcctc
aaggagaatg gccccatggc ctctgaccca ctctgcctga cctactccta cctttctcat
gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag
ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc
tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat
gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc
ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg
acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac
agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg
gacctcggac agttcctgct gttctgccac atcagctccc accagcatga tggcatggag
gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag
gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat
gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc
tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc
cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc
aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc
attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg
ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact
gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc
cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca
accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg
gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag
aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag
aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg
cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg
tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct
attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag
atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc
atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc
atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac
agctatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccagg
(SEQ ID NO:3)

Figure 4

CS04-LC-NA

g agatcaccag gaccaccctc
cagtctgacc aggaggagat tgactatgat gacaccattt ctgtggagat gaagaaagag
gactttgaca tctatgacga ggacgagaac cagagcccaa ggagcttcca gaagaagacc
aggcactact tcattgctgc tgtggagcgc ctgtgggact atggcatgag ctccagcccc
catgtcctca ggaacagggc ccagtctggc tctgtgccac agttcaagaa agtggtcttc
caagagttca ctgatggcag cttcacccag cccctgtaca gaggggagct gaatgagcac
ctgggactcc tgggcccata catcagggct gaggtggagg acaacatcat ggtgaccttc
cgcaaccagg cctccaggcc ctacagcttc tacagctccc tcatcagcta tgaggaggac
cagaggcagg gggctgagcc acgcaagaac tttgtgaaac ccaatgaaac caagacctac
ttctggaaag tccagcacca catggccccc accaaggatg agtttgactg caaggcctgg
gcctacttct ctgatgtgga cctggagaag gatgtgcact ctggcctgat tggcccactc
ctggtctgcc acaccaacac cctgaaccct gcccatggaa ggcaagtgac tgtgcaggag
tttgccctct tcttcaccat ctttgatgaa accaagagct ggtacttcac tgagaacatg
gagcgcaact gcagggcccc atgcaacatt cagatggagg accccacctt caaagagaac
taccgcttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggcc
caggaccaga ggatcaggtg gtacctgctt tctatgggct ccaatgagaa cattcactcc
atccacttct ctgggcatgt cttcactgtg cgcaagaagg aggagtacaa gatggccctg
tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc
tggagggtgg agtgcctcat tggggagcac ctgcatgctg gcatgagcac cctgttcctg
gtctacagca acaagtgcca gacccccctg ggaatggcct ctggccacat cagggacttc
cagatcactg cctctggcca gtatggccag tgggccccca agctggccag gctccactac
tctggatcca tcaatgcctg gagcaccaag gagccattca gctggatcaa agtggacctg
ctggccccca tgatcatcca tggcatcaag acccaggggg ccaggcagaa gttctccagc
ctgtacatca gccagttcat catcatgtac agcctggatg gcaagaaatg gcagacctac
agaggcaact ccactggaac actcatggtc ttctttggca atgtggacag ctctggcatc
aagcacaaca tcttcaaccc cccaatcatc gccagataca tcaggctgca ccccacccac
tacagcatcc gcagcaccct caggatggag ctgatgggct gtgacctgaa ctcctgcagc
atgccctgg gcatggagag caaggccatt tctgatgccc agatcactgc ctccagctac
ttcaccaaca tgtttgccac ctggagccca agcaaggcca ggctgcacct ccagggaagg
agcaatgcct ggaggcccca ggtcaacaac ccaaaggagt ggctgcaggt ggacttccag
aagaccatga aggtcactgg ggtgaccacc caggggtca agagcctgct caccagcatg
tatgtgaagg agttcctgat cagctccagc caggatggcc accagtggac cctcttcttc
cagaatggca aggtcaaggt gttccagggc aaccaggaca gcttcacccc tgtggtgaac
agcctggacc ccccctcct gaccagatac ctgaggattc accccagag ctgggtccac
cagattgccc tgaggatgga ggtcctggga tgtgaggccc aggacctgta c
(SEQ ID NO:4)

Figure 5

BDLO01 - agc ttctctcaga atccacctgt cctgaagaga caccagaga (SEQ ID NO:5)

BDLO04 - agc ttcagccaga atccacctgt cctgaaacgc caccagagg (SEQ ID NO:6)

BDLO23 - agc ttcagccaga accccccegt gctgaagagg caccagagg (SEQ ID NO:7)

BDLNG1 - agcttcagccagaatGTGAGCAACAATGTGAGCAACAATGCCACCAATAATGCTACCAACccacctgtcctgaaacgccaccagagg (SEQ ID NO:36)

BDLNG4 - agcttcagccagaatGTGAGCAACAATGCCACCAACAATGTGAGCAACccacctgtcctgaaacgccaccagagg (SEQ ID NO:37)

BDLNG5 - agcttcagccagaatGTGAGCAATAATGCCACCAACccacctgtcctgaaacgccaccagagg (SEQ ID NO:38)

BDLNG6 - agcttcagccagaatGTGAGCAATAATccacctgtcctgaaacgccaccagagg (SEQ ID NO:39)

BDLNG9 - agcttcagccagaatAGGAGCCTGccacctgtcctgaaacgccaccagagg (SEQ ID NO:40)

BDLNG10 - agcttcagccagaatGCCACTAATGTGTCTAACAACTCTGCTACCTCTGCTGACTCTGCTGTGAGCccacctgtcctgaaacgccaccagagg
(SEQ ID NO:41)

BDLNG16 - agcttcagccagaatGCCACCAACTATGTGAACAGGAGCCTGccacctgtcctgaaacgccaccagagg
(SEQ ID NO:42)

BDLNG17 - agcttcagccagaatGCCACCAACTATGTGAACAGGAGCCTGTCTGCCACCTCTGCTGACTCTGCTGTGAGCCAGAATccacctgtcctgaaacgccaccag
agg(SEQ ID NO:43)

BDLNG18 - agcttcagccagaatGTGAGCAACAATGTGAGCAATGCTGTGTCTGCTGTGTCTGCTccacctgtcctgaaacgccaccagagg (SEQ ID NO:44)

BDLNG19 - agcttcagccagaatATCACTGTGGCCTCTGCCACCTCTAACATCACTGTGGCCTCTGCTGACCccacctgtcctgaaacgccaccagagg
(SEQ ID NO:45)

BDLNG20 - agcttcagccagaatATCACTGTGACCAACATCACTGTGACTGCCccacctgtcctgaaacgccaccagagg (SEQ ID NO:46)

BDLNG21 - agcttcagccagaatCAGACTGTGACCAACATCACTGTGACTGCCccacctgtcctgaaacgccaccagagg (SEQ ID NO:47)

BDLNGV - agcttcagccagaatGCCACTAATGTGTCTAACAACAGCAACACCAGCAATGACAGCAATGTGTCTccacctgtcctgaaacgccaccagagg
(SEQ ID NO:48)

Figure 6

CS04-AV-NA

```
1    tcgcgcgttt cggtgatgac ggtgaaaacc tctgacacat gcagctcccg gagacggtca
61   cagcttgtct gtaagcggat gccgggagca gacaagcccg tcagggcgcg tcagcgggtg
121  ttggcgggtg tcggggctgg cttaactatg cggcatcaga gcagattgta ctgagagtgc
181  accatatgcg gtgtgaaata ccgcacagat gcgtaaggag aaaataccgc atcaggcgcc
241  attcgccatt caggctgcgc aactgttggg aagggcgatc ggtgcgggcc tcttcgctat
301  tacgccagct ggcgaaaggg ggatgtgctg caaggcgatt aagttgggta acgccagggt
361  tttcccagtc acgacgttgt aaaacgacgg ccagtgaatt cctcgagatt taaatgacgt
421  tggccactcc ctctctgcgc gctcgctcgc tcactgaggc cgggcgacca aaggtcgccc
481  gacgcccggg ctttgcccgg gcggcctcag tgagcgagcg agcgcgcaga gagggagtgg
541  ccaactccat cactaggggt tcctgagttt aaacttcgtc gacgattcga gcttgggctg
601  caggtcgagg gcactgggag gatgttgagt aagatggaaa actactgatg acccttgcag
661  agacagagta ttaggacatg tttgaacagg ggccgggcga tcagcaggta gctctagagg
721  atccccgtct gtctgcacat ttcgtagagc gagtgttccg atactctaat ctcccttaggc
781  aaggttcata tttgtgtagg ttacttattc tccttttgtt gactaagtca ataatcagaa
841  tcagcaggtt tggagtcagc ttggcaggga tcagcagcct gggttggaag gaggggtat
901  aaaagccccc tcaccaggag aagccgtcac acagactagg cgcgccaccg ccaccatgca
961  gattgagctg agcacctgct tcttcctgtg cctgctgagg ttctgcttct ctgccaccag
1021 gagatactac ctgggggctg tggagctttc ttgggactac atgcagtctg acctgggggga
1081 gctgcctgtg gatgccaggt tcccacccag agtgcccaaa tccttcccat tcaacacctc
1141 tgtggtctac aagaagaccc tctttgtgga gttcactgac cacctgttca acattgccaa
1201 acccaggcca ccctggatgg gactcctggg acccaccatt caggctgagg tgtatgacac
1261 tgtggtcatc accctcaaga acatggcctc ccaccctgtg agcctgcatg ctgtgggggt
1321 cagctactgg aaggcctctg agggggctga gtatgatgac cagacctccc agagggagaa
1381 ggaggatgac aaagtgttcc ctgggggcag ccacacctat gtgtggcagg tcctcaagga
1441 gaatggcccc atggcctctg acccactctg cctgacctac tcctacctttt ctcatgtgga
1501 cctggtcaag gacctcaact ctggactgat tggggccctg ctggtgtgca gggagggctc
1561 cctggccaaa gagaagaccc agaccctgca caagttcatt ctcctgtttg ctgtctttga
1621 tgagggcaag agctggcact ctgaaaccaa gaactccctg atgcaggaca gggatgctgc
1681 ctctgccagg gcctggccca agatgcacac tgtgaatggc tatgtgaaca ggagcctgcc
1741 tggactcatt ggctgccaca ggaaatctgt ctactggcat gtgattggca tggggacaac
1801 ccctgaggtg cactccattt tcctggaggg ccacaccttc ctggtcagga accacagaca
1861 ggccagcctg gagatcagcc ccatcacctt cctcactgcc cagaccctgc tgatggacct
1921 cggacagttc ctgctgttct gccacatcag ctcccaccag catgatggca tggaggccta
1981 tgtcaaggtg gacagctgcc ctgaggagcc acagctcagg atgaagaaca atgaggaggc
2041 tgaggactat gatgatgacc tgactgactc tgagatggat gtggtccgct ttgatgatga
2101 caacagccca tccttcattc agatcaggtc tgtggccaag aaacacccca agacctgggt
2161 gcactacatt gctgctgagg aggaggactg ggactatgcc ccactggtcc tggccctga
2221 tgacaggagc tacaagagcc agtacctcaa caatggccca cagaggattg gacgcaagta
2281 caagaaagtc aggttcatgg cctacactga tgaaaccttc aagaccaggg aggccattca
2341 gcatgagtct ggcatcctgg gcccactcct gtatggggag gtgggggaca ccctgctcat
2401 catcttcaag aaccaggcct ccaggcccta caacatctac ccacatggca tcactgatgt
2461 caggccctg tacagccgca ggctgccaaa gggggtgaaa cacctcaagg acttccccat
```

Figure 7A

```
2521 tctgcctggg gagatcttca agtacaagtg gactgtcact gtggaggatg gaccaaccaa
2581 atctgacccc aggtgcctca ccagatacta ctccagcttt gtgaacatgg agagggacct
2641 ggcctctggc ctgattggcc cactgctcat ctgctacaag gagtctgtgg accagagggg
2701 aaaccagatc atgtctgaca agaggaatgt gattctgttc tctgtctttg atgagaacag
2761 gagctggtac ctgactgaga acattcagcg cttcctgccc aaccctgctg gggtgcagct
2821 ggaggaccct gagttccagg ccagcaacat catgcactcc atcaatggct atgtgtttga
2881 cagcctccag ctttctgtct gcctgcatga ggtggcctac tggtacattc tttctattgg
2941 ggcccagact gacttccttt ctgtcttctt ctctggctac accttcaaac acaagatggt
3001 gtatgaggac accctgaccc tcttcccatt ctctggggag actgtgttca tgagcatgga
3061 gaaccctggc ctgtggattc tgggatgcca caactctgac ttccgcaaca ggggcatgac
3121 tgccctgctc aaagtctcct cctgtgacaa gaacactggg gactactatg aggacagcta
3181 tgaggacatc tctgcctacc tgctcagcaa gaacaatgcc attgagccca ggagcttcag
3241 ccagaatcca cctgtcctga aacgccacca gagggagatc accaggacca ccctccagtc
3301 tgaccaggag gagattgact atgatgacac catttctgtg gagatgaaga aagaggactt
3361 tgacatctat gacgaggacg agaaccagag cccaaggagc ttccagaaga agaccaggca
3421 ctacttcatt gctgctgtgg agcgcctgtg ggactatggc atgagctcca gccccatgt
3481 cctcaggaac agggcccagt ctggctctgt gccacagttc aagaaagtgg tcttccaaga
3541 gttcactgat ggcagcttca cccagccct gtacagaggg gagctgaatg agcacctggg
3601 actcctgggc ccatacatca gggctgaggt ggaggacaac atcatggtga ccttccgcaa
3661 ccaggcctcc aggccctaca gcttctacag ctccctcatc agctatgagg aggaccagag
3721 gcaggggct gagccacgca agaactttgt gaaacccaat gaaaccaaga cctacttctg
3781 gaaagtccag caccacatgg ccccaccaa ggatgagttt gactgcaagg cctgggccta
3841 cttctctgat gtggacctgg agaaggatgt gcactctggc ctgattggcc cactcctggt
3901 ctgccacacc aacaccctga accctgccca tggaaggcaa gtgactgtgc aggagtttgc
3961 cctcttcttc accatctttg atgaaaccaa gagctggtac ttcactgaga acatggagcg
4021 caactgcagg gccccatgca acattcagat ggaggacccc accttcaaag agaactaccg
4081 cttccatgcc atcaatggct acatcatgga caccctgcct gggcttgtca tggcccagga
4141 ccagaggatc aggtggtacc tgctttctat gggctccaat gagaacattc actccatcca
4201 cttctctggg catgtcttca ctgtgcgcaa gaaggaggag tacaagatgg ccctgtacaa
4261 cctctaccct ggggtctttg agactgtgga gatgctgccc tccaaagctg gcatctggag
4321 ggtggagtgc ctcattgggg agcacctgca tgctggcatg agcaccctgt tcctggtcta
4381 cagcaacaag tgccagaccc ccctgggaat ggcctctggc cacatcaggg acttccagat
4441 cactgcctct ggccagtatg gccagtgggc ccccaagctg gccaggctcc actactctgg
4501 atccatcaat gcctggagca ccaaggagcc attcagctgg atcaaagtgg acctgctggc
4561 ccccatgatc atccatggca tcaagaccca gggggccagg cagaagttct ccagcctgta
4621 catcagccag ttcatcatca tgtacagcct ggatggcaag aaatggcaga cctacagagg
4681 caactccact ggaacactca tggtcttctt tggcaatgtg gacagctctg gcatcaagca
4741 caacatcttc aacccccaa tcatcgccag atacatcagg ctgcacccca ccccactacag
4801 catccgcagc accctcagga tggagctgat gggctgtgac ctgaactcct gcagcatgcc
4861 cctgggcatg gagagcaagg ccatttctga tgcccagatc actgcctcca gctacttcac
4921 caacatgttt gccacctgga gcccaagcaa ggccaggctg cacctccagg gaaggagcaa
4981 tgcctggagg ccccaggtca acaacccaaa ggagtggctg caggtggact tccagaagac
```

Figure 7B

```
5041 catgaaggtc actggggtga ccacccaggg ggtcaagagc ctgctcacca gcatgtatgt
5101 gaaggagttc ctgatcagct ccagccagga tggccaccag tggaccctct tcttccagaa
5161 tggcaaggtc aaggtgttcc agggcaacca ggacagcttc acccctgtgg tgaacagcct
5221 ggaccccccc ctcctgacca gatacctgag gattcacccc cagagctggg tccaccagat
5281 tgccctgagg atggaggtcc tgggatgtga ggccccaggac ctgtactgat gacgagcggc
5341 cgctcttagt agcagtatcg ataataaaag atctttattt tcattagatc tgtgtgttgg
5401 tttttgtgt gttaattaag ctcgcgaagg aacccctagt gatggagttg gccactccct
5461 ctctgcgcgc tcgctcgctc actgaggccg ggcgaccaaa ggtcgcccga cgcccgggct
5521 ttgccccggc ggcctcagtg agcgagcgag cgcgcagaga gggagtggcc aagacgattt
5581 aaatgacaag cttggcgtaa tcatggtcat agctgtttcc tgtgtgaaat tgttatccgc
5641 tcacaattcc acacaacata cgagccggaa gcataaagtg taaagcctgg ggtgcctaat
5701 gagtgagcta actcacatta attgcgttgc gctcactgcc cgctttccag tcgggaaacc
5761 tgtcgtgcca gctgcattaa tgaatcggcc aacgcgcggg gagaggcggt ttgcgtattg
5821 ggcgctcttc cgcttcctcg ctcactgact cgctgcgctc ggtcgttcgg ctgcggcgag
5881 cggtatcagc tcactcaaag gcggtaatac ggttatccac agaatcaggg gataacgcag
5941 gaaagaacat gtgagcaaaa ggccagcaaa aggccaggaa ccgtaaaaag gccgcgttgc
6001 tggcgttttt ccataggctc cgcccccctg acgagcatca caaaaatcga cgctcaagtc
6061 agaggtggcg aaacccgaca ggactataaa gataccaggc gtttcccccc ggaagctccc
6121 tcgtgcgctc tcctgttccg accctgccgc ttaccggata cctgtccgcc tttctccctt
6181 cgggaagcgt ggcgcttttct catagctcac gctgtaggta tctcagttcg gtgtaggtcg
6241 ttcgctccaa gctgggctgt gtgcacgaac cccccgttca gcccgaccgc tgcgccttat
6301 ccggtaacta tcgtcttgag tccaacccgg taagacacga cttatcgcca ctggcagcag
6361 ccactggtaa caggattagc agagcgaggt atgtaggcgg tgctacagag ttcttgaagt
6421 ggtggcctaa ctacggctac actagaagaa cagtatttgg tatctgcgct ctgctgaagc
6481 cagttacctt cggaaaaaga gttggtagct cttgatccgg caaacaaacc accgctggta
6541 gcggtggttt ttttgtttgc aagcagcaga ttacgcgcag aaaaaaagga tctcaagaag
6601 atcctttgat cttttctacg gggtctgacg ctcagtggaa cgaaaactca cgttaaggga
6661 ttttggtcat gagattatca aaaaggatct tcacctagat ccttttaaat taaaaatgaa
6721 gttttaaatc aatctaaagt atatatgagt aaacttggtc tgacagttac caatgcttaa
6781 tcagtgaggc acctatctca gcgatctgtc tatttcgttc atccatagtt gcctgactcc
6841 ccgtcgtgta gataactacg atacgggagg gcttaccatc tggccccagt gctgcaatga
6901 taccgcgaga cccacgctca ccggctccag atttatcagc aataaaccag ccagccggaa
6961 gggccgagcg cagaagtggt cctgcaactt tatccgcctc catccagtct attaattgtt
7021 gccgggaagc tagagtaagt agttcgccag ttaatagttt gcgcaacgtt gttgccattg
7081 ctacaggcat cgtggtgtca cgctcgtcgt ttggtatggc ttcattcagc tccggttccc
7141 aacgatcaag gcgagttaca tgatcccccа tgttgtgcaa aaaagcggtt agctccttcg
7201 gtcctccgat cgttgtcaga agtaagttgg ccgcagtgtt atcactcatg gttatggcag
7261 cactgcataa ttctcttact gtcatgccat ccgtaagatg cttttctgtg actggtgagt
7321 actcaaccaa gtcattctga gaatagtgta tgcggcgacc gagttgctct tgcccggcgt
7381 caatacggga taataccgcg ccacatagca gaactttaaa agtgctcatc attggaaaac
7441 gttcttcggg gcgaaaactc tcaaggatct taccgctgtt gagatccagt tcgatgtaac
7501 ccactcgtgc acccaactga tcttcagcat cttttacttt caccagcgtt tctgggtgag
7561 caaaaacagg aaggcaaaat gccgcaaaaa agggaataag ggcgacacgg aaatgttgaa
7621 tactcatact cttccttttt caatattatt gaagcattta tcagggttat tgtctcatga
7681 gcggatacat atttgaatgt atttagaaaa ataaacaaat aggggttccg cgcacatttc
7741 cccgaaaagt gccacctgac gtctaagaaa ccattattat catgacatta acctataaaa
7801 ataggcgtat cacgaggccc tttcgtc  (SEQ ID NO:8)
```

Figure 7C

CS01m1-FL-NA

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGGA
GATACTACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCTGT
GGATGCCAGGTTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAGAAG
ACACTCTTTGTGGAATTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATGGGAC
TCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATGGCATC
CCACCCTGTGTCTCTGCATGCTGTGGGAGTCTCATACTGGAAAGCCTCTGAAGGGGCTGAGTATGAT
GACCAGACATCCCAGAGAGAGAAAGAGGATGACAAGGTGTTCCCTGGGGGATCTCACACCTATGTGT
GGCAAGTCCTCAAGGAGAATGGACCCATGGCATCTGACCCACTCTGCCTGACATACTCCTACCTTTC
TCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCACTGCTGGTGTGCAGGGAAGGA
TCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTCCTGTTTGCTGTCTTTGATGAGG
GCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGATGCTGCCTCTGCCAGGGC
ATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTCATTGGCTGCCAC
AGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCACTCCATTTTCCTGG
AGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCTCCCATCACCTTCCT
CACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTCCTGCCACATCTCTTCCCACCAG
CATGATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCACAGCTCAGGATGAAGA
ACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATGGATGTGGTCAGATTTGA
TGATGACAACTCTCCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAACACCCCAAGACATGGGTG
CACTACATTGCTGCTGAGGAAGAGGACTGGGACTATGCACCACTGGTCCTGGCCCCTGATGACAGGA
GCTACAAGTCTCAGTACCTCAACAATGGCCCACAAAGAATTGGAAGAAAGTACAAGAAAGTCAGATT
CATGGCCTACACTGATGAAACCTTCAAGACAAGAGAAGCCATTCAGCATGAGTCTGGCATTCTGGGA
CCACTCCTGTATGGGGAAGTGGGAGACACCCTGCTCATCATCTTCAAGAACCAGGCCTCCAGGCCCT
ACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTACAGCAGGAGACTGCCAAAAGGGGT
GAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTCAAGTACAAGTGGACTGTCACTGTG
GAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGATACTACTCCTCTTTTGTGAACATGG
AGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATCTGCTACAAGGAGTCTGTGGACCAGAG
AGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTGTTCTCTGTCTTTGATGAGAACAGATCA
TGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAACCCTGCTGGGGTGCAACTGGAAGACCCTG
AGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGCTATGTGTTTGACTCTCTCCAGCTTTCTGT
CTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCTATTGGGGCACAAACTGACTTCCTTTCTGTC
TTCTTCTCTGGATACACCTTCAAGCACAAGATGGTGTATGAGGACACCCTGACACTCTTCCCATTCT
CTGGGGAAACTGTGTTCATGAGCATGGAGAACCCTGGACTGTGGATTCTGGGATGCCACAACTCTGA
CTTCAGAAACAGGGGAATGACTGCACTGCTCAAAGTCTCCTCCTGTGACAAGAACACTGGGGACTAC
TATGAGGACTCTTATGAGGACATCTCTGCCTACCTGCTCAGCAAGAACAATGCCATTGAGCCCAGAA
GCTTCTCTCAGAATCCACCTGTCCTGAAGAGACACCAGAGAGAGATCACCAGGACAACCCTCCAGTC
TGACCAGGAAGAGATTGACTATGATGACACCATTTCTGTGGAGATGAAGAAGGAGGACTTTGACATC
TATGATGAGGACGAGAACCAGTCTCCAAGATCATTCCAGAAGAAGACAAGACACTACTTCATTGCTG
CTGTGGAAAGACTGTGGGACTATGGCATGTCTTCCTCTCCCCATGTCCTCAGGAACAGGGCACAGTC
TGGCTCTGTGCCACAGTTCAAGAAAGTGGTCTTCCAGGAGTTCACTGATGGCTCATTCACCCAGCCC
CTGTACAGAGGGGAACTGAATGAGCACCTGGGACTCCTGGGACCATACATCAGGGCTGAGGTGGAAG
ACAACATCATGGTGACATTCAGAAACCAGGCCTCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAG
CTATGAGGAAGACCAGAGACAAGGGGCTGAGCCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAG
ACCTACTTCTGGAAAGTCCAGCACCACATGGCACCCACCAAGGATGAGTTTGACTGCAAGGCCTGGG

(Continued)

Figure 8A

CATACTTCTCTGATGTGGACCTGGAGAAAGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTG
CCACACCAACACCCTGAACCCTGCACATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTC
ACCATCTTTGATGAAACCAAGTCATGGTACTTCACTGAGAACATGGAGAGAAACTGCAGAGCACCAT
GCAACATTCAGATGGAAGACCCCACCTTCAAGGAGAACTACAGGTTCCATGCCATCAATGGCTACAT
CATGGACACCCTGCCTGGGCTTGTCATGGCACAGGACCAGAGAATCAGATGGTACCTGCTTTCTATG
GGATCCAATGAGAACATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAGG
AATACAAGATGGCCCTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAA
AGCTGGCATCTGGAGGGTGGAATGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTC
CTGGTCTACAGCAACAAGTGCCAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGA
TCACTGCCTCTGGCCAGTATGGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCAT
CAATGCATGGTCAACCAAGGAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATT
CATGGCATCAAGACACAGGGGGCAAGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCA
TGTACTCTCTGGATGGCAAGAAGTGGCAGACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTT
CTTTGGCAATGTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCTCCCATCATTGCCAGATAC
ATCAGGCTGCACCCCACCCACTACTCAATCAGATCAACCCTCAGGATGGAACTGATGGGATGTGACC
TGAACTCCTGCTCAATGCCCCTGGGAATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCATC
CTCTTACTTCACCAACATGTTTGCCACCTGGTCACCATCAAAAGCCAGGCTGCACCTCCAGGGAAGA
AGCAATGCCTGGAGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGACTTCCAGAAGACAA
TGAAAGTCACTGGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTGAAGGAGTT
CCTGATCTCTTCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAGGTG
TTCCAGGGCAACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGAT
ACCTGAGAATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGTGA
GGCACAAGACCTGTACTGA (SEQ ID NO:49)

Figure 8B

CS04Δ(760-1667) - CS04-SC1-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGGAGATAC
TACCTGGGGGCTGTGGAGCTTTCTTGGGACTACATGCAGTCTGACCTGGGGGAGCTGCCTGTGGATGCCAGG
TTCCCACCCAGAGTGCCCAAATCCTTCCCATTCAACACCTCTGTGGTCTACAAGAAGACCCTCTTTGTGGAG
TTCACTGACCACCTGTTCAACATTGCCAAACCCAGGCCCACCCTGGATGGGACTCCTGGGACCCACCATTCAG
GCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATGGCCTCCCACCCTGTGAGCCTGCATGCTGTG
GGGGTCAGCTACTGGAAGGCCTCTGAGGGGGCTGAGTATGATGACCAGACCTCCCAGAGGGAGAAGGAGGAT
GACAAAGTGTTCCCTGGGGGCAGCCACACCTATGTGTGGCAGGTCCTCAAGGAGAATGGCCCCATGGCCTCT
GACCCACTCTGCCTGACCTACTCCTACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATT
GGGGCCCTGCTGGTGTGCAGGGAGGGCTCCCTGGCCAAAGAGAAGACCCAGACCCTGCACAAGTTCATTCTC
CTGTTTGCTGTCTTTGATGAGGGCAAGAGCTGGCACTCTGAAACCAAGAACTCCCTGATGCAGGACAGGGAT
GCTGCCTCTGCCAGGGCCTGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGGAGCCTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAGGTGCACTCCATT
TTCCTGGAGGGCCACACCTTCCTGGTCAGGAACCACAGACAGGCCAGCCTGGAGATCAGCCCCATCACCTTC
CTCACTGCCCAGACCCTGCTGATGGACCTCGGACAGTTCCTGCTGTTCTGCCACATCAGCTCCCACCAGCAT
GATGGCATGGAGGCCTATGTCAAGGTGGACAGCTGCCCTGAGGAGCCACAGCTCAGGATGAAGAACAATGAG
GAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATGGATGTGGTCCGCTTTGATGATGACAACAGC
CCATCCTTCATTCAGATCAGGTCTGTGGCCAAGAAACACCCCAAGACCTGGGTGCACTACATTGCTGCTGAG
GAGGAGGACTGGGACTATGCCCCACTGGTCCTGGCCCCTGATGACAGGAGCTACAAGAGCCAGTACCTCAAC
AATGGCCCACAGAGGATTGGACGCAAGTACAAGAAAGTCAGGTTCATGGCCTACACTGATGAAACCTTCAAG
ACCAGGGAGGCCATTCAGCATGAGTCTGGCATCCTGGGCCCACTCCTGTATGGGGAGGTGGGGGACACCCTG
CTCATCATCTTCAAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCC
CTGTACAGCCGCAGGCTGCCAAAGGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGGGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACCAAATCTGACCCCAGGTGCCTCACCAGATACTAC
TCCAGCTTTGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATTGGCCCACTGCTCATCTGCTACAAGGAG
TCTGTGGACCAGAGGGGAAACCAGATCATGTCTGACAAGAGGAATGTGATTCTGTTCTCTGTCTTTGATGAG
AACAGGAGCTGGTACCTGACTGAGAACATTCAGCGCTTCCTGCCCAACCCTGCTGGGGTGCAGCTGGAGGAC
CCTGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGCTATGTGTTTGACAGCCTCCAGCTTTCTGTC
TGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCTATTGGGGCCCAGACTGACTTCCTTTCTGTCTTCTTC
TCTGGCTACACCTTCAAACACAAGATGGTGTATGAGGACACCCTGACCCTCTTCCCATTCTCTGGGGAGACT
GTGTTCATGAGCATGGAGAACCCTGGCCTGTGGATTCTGGGATGCCACAACTCTGACTTCCGCAACAGGGGC
ATGACTGCCCTGCTCAAAGTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACAGCTATGAGGAC
ATCTCTGCCTACCTGCTCAGCAAGAACAATGCCATTGAGCCCAGGGAGATCACCAGGACCACCCTCCAGTCT
GACCAGGAGGAGATTGACTATGATGACACCATTTCTGTGGAGATGAAGAAAGAGGACTTTGACATCTATGAC
GAGGACGAGAACCAGAGCCCAAGGAGCTTCCAGAAGAAGACCAGGCACTACTTCATTGCTGCTGTGGAGCGC
CTGTGGGACTATGGCATGAGCTCCAGCCCCCATGTCCTCAGGAACAGGGCCCAGTCTGGCTCTGTGCCACAG
TTCAAGAAAGTGGTCTTCCAAGAGTTCACTGATGGCAGCTTCACCCAGCCCCTGTACAGAGGGGAGCTGAAT
GAGCACCTGGGACTCCTGGGCCCATACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACCTTCCGCAAC
CAGGCCTCCAGGCCCTACAGCTTCTACAGCTCCCTCATCAGCTATGAGGAGGACCAGAGGCAGGGGGCTGAG
CCACGCAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCACCACATGGCCCCC

(Continued)

Figure 9A

ACCAAGGATGAGTTTGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTGGAGAAGGATGTGCACTCT
GGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCTGCCCATGGAAGGCAAGTGACTGTG
CAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAGAGCTGGTACTTCACTGAGAACATGGAGCGC
AACTGCAGGGCCCCATGCAACATTCAGATGGAGGACCCCACCTTCAAAGAGAACTACCGCTTCCATGCCATC
AATGGCTACATCATGGACACCCTGCCTGGGCTTGTCATGGCCCAGGACCAGAGGATCAGGTGGTACCTGCTT
TCTATGGGCTCCAATGAGAACATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGCGCAAGAAGGAG
GAGTACAAGATGGCCCTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCT
GGCATCTGGAGGGTGGAGTGCCTCATTGGGGAGCACCTGCATGCTGGCATGAGCACCCTGTTCCTGGTCTAC
AGCAACAAGTGCCAGACCCCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGC
CAGTATGGCCAGTGGGCCCCCAAGCTGGCCAGGCTCCACTACTCTGGATCCATCAATGCCTGGAGCACCAAG
GAGCCATTCAGCTGGATCAAAGTGGACCTGCTGGCCCCCATGATCATCCATGGCATCAAGACCCAGGGGGCC
AGGCAGAAGTTCTCCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGATGGCAAGAAATGGCAG
ACCTACAGAGGCAACTCCACTGGAACACTCATGGTCTTCTTTGGCAATGTGGACAGCTCTGGCATCAAGCAC
AACATCTTCAACCCCCCAATCATCGCCAGATACATCAGGCTGCACCCCACCCACTACAGCATCCGCAGCACC
CTCAGGATGGAGCTGATGGGCTGTGACCTGAACTCCTGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATT
TCTGATGCCCAGATCACTGCCTCCAGCTACTTCACCAACATGTTTGCCACCTGGAGCCCAAGCAAGGCCAGG
CTGCACCTCCAGGGAAGGAGCAATGCCTGGAGGCCCCAGGTCAACAACCCAAAGGAGTGGCTGCAGGTGGAC
TTCCAGAAGACCATGAAGGTCACTGGGGTGACCACCCAGGGGGTCAAGAGCCTGCTCACCAGCATGTATGTG
AAGGAGTTCCTGATCAGCTCCAGCCAGGATGGCCACCAGTGGACCCTCTTCTTCCAGAATGGCAAGGTCAAG
GTGTTCCAGGGCAACCAGGACAGCTTCACCCCTGTGGTGAACAGCCTGGACCCCCCCCTCCTGACCAGATAC
CTGAGGATTCACCCCCAGAGCTGGGTCCACCAGATTGCCCTGAGGATGGAGGTCCTGGGATGTGAGGCCCAG
GACCTGTACTGA (SEQ ID NO:9)

Figure 9B

CS04Δ(760-1667) - CS04-SC1-AA

MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYKK
TLFVEFTDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYD
DQTSQREKEDDKVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREG
SLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCH
RKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLFCHISSHQ
HDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKKHPKTWV
HYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQHESGILG
PLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIFKYKWTVTV
EDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVILFSVFDENRS
WYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILSIGAQTDFLSV
FFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGDY
YEDSYEDISAYLLSKNNAIEPREITRTTLQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQK
KTRHYFIAAVERLWDYGMSSSPHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLG
PYIRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTK
DEFDCKAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTEN
MERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIHSIHFSGH
VFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKCQTPLGMA
SGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDLLAPMIIHGIKTQGARQKFSS
LYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNIFNPPIIARYIRLHPTHYSIRSTL
RMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEW
LQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSSQDGHQWTLFFQNGKVKVFQGNQDSFTPVVNS
LDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY (SEQ ID NO:10)

Figure 10

CS04Δ(772-1667) - CS04-SC2-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAGCTTTCTTGGGACTACATGCAGTCTGACCTGGGGGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAATCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACCCTCTTTGTGGAGTTCACTGACCACCTGTTCAACATTGCCAAACCCAGGCCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATG
GCCTCCCACCCTGTGAGCCTGCATGCTGTGGGGGTCAGCTACTGGAAGGCCTCTGAGGGGGCTGAG
TATGATGACCAGACCTCCCAGAGGGAGAAGGAGGATGACAAAGTGTTCCCTGGGGGCAGCCACACC
TATGTGTGGCAGGTCCTCAAGGAGAATGGCCCCATGGCCTCTGACCCACTCTGCCTGACCTACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCCCTGCTGGTGTGC
AGGGAGGGCTCCCTGGCCAAAGAGAAGACCCAGACCCTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGAGCTGGCACTCTGAAACCAAGAACTCCCTGATGCAGGACAGGGATGCTGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGGAGCCTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAGGTGCAC
TCCATTTTCCTGGAGGGCCACACCTTCCTGGTCAGGAACCACAGACAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTCACTGCCCAGACCCTGCTGATGGACCTCGGACAGTTCCTGCTGTTCTGCCAC
ATCAGCTCCCACCAGCATGATGGCATGGAGGCCTATGTCAAGGTGGACAGCTGCCCTGAGGAGCCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCCGCTTTGATGATGACAACAGCCCATCCTTCATTCAGATCAGGTCTGTGGCCAAGAAA
CACCCCAAGACCTGGGTGCACTACATTGCTGCTGAGGAGGAGGACTGGGACTATGCCCCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGAGCCAGTACCTCAACAATGGCCCACAGAGGATTGGACGC
AAGTACAAGAAAGTCAGGTTCATGGCCTACACTGATGAAACCTTCAAGACCAGGGAGGCCATTCAG
CATGAGTCTGGCATCCTGGGCCCACTCCTGTATGGGGAGGTGGGGGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCCGCAGGCTGCCAAAGGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGGGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACCAAATCTGACCCCAGGTGCCTCACCAGA
TACTACTCCAGCTTTGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATTGGCCCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGGGGAAACCAGATCATGTCTGACAAGAGGAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGGAGCTGGTACCTGACTGAGAACATTCAGCGCTTCCTGCCCAAC
CCTGCTGGGGTGCAGCTGGAGGACCCTGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACAGCCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCCCAGACTGACTTCCTTTCTGTCTTCTTCTCTGGCTACACCTTCAAACACAAGATGGTG
TATGAGGACACCCTGACCCTCTTCCCATTCTCTGGGGAGACTGTGTTCATGAGCATGGAGAACCCT
GGCCTGTGGATTCTGGGATGCCACAACTCTGACTTCCGCAACAGGGGCATGACTGCCCTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACAGCTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATGCCATTGAGCCCAGGAGCTTCAGCCAGAATTCCAGACACCCCAGCACC
AGGGAGATCACCAGGACCACCCTCCAGTCTGACCAGGAGGAGATTGACTATGATGACACCATTTCT
GTGGAGATGAAGAAAGAGGACTTTGACATCTATGACGAGGACGAGAACCAGAGCCCAAGGAGCTTC

(Continued)

Figure 11A

CAGAAGAAGACCAGGCACTACTTCATTGCTGCTGTGGAGCGCCTGTGGGACTATGGCATGAGCTCC
AGCCCCCATGTCCTCAGGAACAGGGCCCAGTCTGGCTCTGTGCCACAGTTCAAGAAAGTGGTCTTC
CAAGAGTTCACTGATGGCAGCTTCACCCAGCCCCTGTACAGAGGGGAGCTGAATGAGCACCTGGGA
CTCCTGGGCCCATACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACCTTCCGCAACCAGGCC
TCCAGGCCCTACAGCTTCTACAGCTCCCTCATCAGCTATGAGGAGGACCAGAGGCAGGGGGCTGAG
CCACGCAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCACCACATG
GCCCCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTGGAGAAG
GATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCTGCCCAT
GGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAGAGCTGG
TACTTCACTGAGAACATGGAGCGCAACTGCAGGGCCCCATGCAACATTCAGATGGAGGACCCCACC
TTCAAAGAGAACTACCGCTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGGCTTGTC
ATGGCCCAGGACCAGAGGATCAGGTGGTACCTGCTTTCTATGGGCTCCAATGAGAACATTCACTCC
ATCCACTTCTCTGGGCATGTCTTCACTGTGCGCAAGAAGGAGGAGTACAAGATGGCCCTGTACAAC
CTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGGAGGGTGGAG
TGCCTCATTGGGGAGCACCTGCATGCTGGCATGAGCACCCTGTTCCTGGTCTACAGCAACAAGTGC
CAGACCCCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGCCAGTAT
GGCCAGTGGGCCCCCAAGCTGGCCAGGCTCCACTACTCTGGATCCATCAATGCCTGGAGCACCAAG
GAGCCATTCAGCTGGATCAAAGTGGACCTGCTGGCCCCCATGATCATCCATGGCATCAAGACCCAG
GGGGCCAGGCAGAAGTTCTCCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGATGGC
AAGAAATGGCAGACCTACAGAGGCAACTCCACTGGAACACTCATGGTCTTCTTTGGCAATGTGGAC
AGCTCTGGCATCAAGCACAACATCTTCAACCCCCCAATCATCGCCAGATACATCAGGCTGCACCCC
ACCCACTACAGCATCCGCAGCACCCTCAGGATGGAGCTGATGGGCTGTGACCTGAACTCCTGCAGC
ATGCCCCTGGGCATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCCTCCAGCTACTTCACC
AACATGTTTGCCACCTGGAGCCCAAGCAAGGCCAGGCTGCACCTCCAGGGAAGGAGCAATGCCTGG
AGGCCCCAGGTCAACAACCCAAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAGGTCACT
GGGGTGACCACCCAGGGGGTCAAGAGCCTGCTCACCAGCATGTATGTGAAGGAGTTCCTGATCAGC
TCCAGCCAGGATGGCCACCAGTGGACCCTCTTCTTCCAGAATGGCAAGGTCAAGGTGTTCCAGGGC
AACCAGGACAGCTTCACCCCTGTGGTGAACAGCCTGGACCCCCCCCCTCCTGACCAGATACCTGAGG
ATTCACCCCCAGAGCTGGGTCCACCAGATTGCCCTGAGGATGGAGGTCCTGGGATGTGAGGCCCAG
GACCTGTACTGA (SEQ ID NO:11)

Figure 11B

CS04Δ(772-1667) - CS04-SC2-AA

MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYKKTLFVEF
TDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEYDDQTSQREKEDDK
VFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCREGSLAKEKTQTLHKFILLFA
VFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEG
HTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNEEAEDY
DDDLTDSEMDVVRFDDDNSPSFIQIRSVAKKHPKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRI
GRKYKKVRFMAYTDETFKTREAIQHESGILGPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLP
KGVKHLKDFPILPGEIFKYKWTVTVEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQ
IMSDKRNVILFSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWY
ILSIGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLKVSSC
DKNTGDYYEDSYEDISAYLLSKNNAIEPRSFSQNSRHPSTREITRTTLQSDQEEIDYDDTISVEMKKEDFDIY
DEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSPHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELN
EHLGLLGPYIRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPT
KDEFDCKAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTENMERNC
RAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIHSIHFSGHVFTVRKKEEYK
MALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLFLVYSNKCQTPLGMASGHIRDFQITASGQYGQ
WAPKLARLHYSGSINAWSTKEPFSWIKVDLLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGN
STGTLMVFFGNVDSSGIKHNIFNPPIIARYIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQIT
ASSYFTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISS
SQDGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY
(SEQ ID NO:12)

Figure 12

NG1: V S N N V S N N A T N N A T N (SEQ ID NO:51)
GTG AGC AAC AAT GTG AGC AAC AAT GCC ACC AAT AAT GCT ACC AAC (SEQ ID NO:50)

NG4: V S N N A T N N V S N (SEQ ID NO:53)
GTG AGC AAC AAT GCC ACC AAC AAT GTG AGC AAC (SEQ ID NO:52)

NG5: V S N N A T N (SEQ ID NO:55)
GTG AGC AAT AAT GCC ACC AAC (SEQ ID NO:54)

NG6: V S N N (SEQ ID NO:57)
GTG AGC AAT AAT (SEQ ID NO:56)

NG9: R S L (SEQ ID NO:59)
AGG AGC CTG (SEQ ID NO:58)

NG10: A T N V S N N S A T S A D S A V S (SEQ ID NO:61)
GCC ACT AAT GTG TCT AAC AAC TCT GCT ACC TCT GCT GAC TCT GCT GTG AGC (SEQ ID NO:60)

NG16: A T N Y V N R S L (SEQ ID NO:63)
GCC ACC AAC TAT GTG AAC AGG AGC CTG (SEQ ID NO:62)

Figure 13A

NG17: A T N Y V N R S L S A T S A D S A V S Q N (SEQ ID NO:65)
GCC ACC AAC TAT GTG AAC AGG AGC CTG TCT GCC ACC TCT GCT GAC TCT GCT GTG AGC CAG AAT (SEQ ID NO:64)

NG18: V S N N V S N A V S A V S A (SEQ ID NO:67)
GTG AGC AAC AAT GTG AGC AAT GCT GTG TCT GCT GTG TCT GCT (SEQ ID NO:66)

NG19: I T V A S A T S N I T V A S A D (SEQ ID NO:69)
ATC ACT GTG GCC TCT GCC ACC TCT AAC ATC ACT GTG GCC TCT GCT GAC (SEQ ID NO:68)

NG20: I T V T N I T V T A (SEQ ID NO:71)
ATC ACT GTG ACC AAC ATC ACT GTG ACT GCC (SEQ ID NO:70)

NG21: Q T V T N I T V T A (SEQ ID NO:73)
CAG ACT GTG ACC AAC ATC ACT GTG ACT GCC (SEQ ID NO:72)

NGV: A T N V S N N S N T S N D S N V S (SEQ ID NO:75)
GCC ACT AAT GTG TCT AAC AAC AGC AAC ACC AGC AAT GAC AGC AAT GTG TCT (SEQ ID NO:74)

Figure 13B

```
# Predictions for N-Glycosylation sites in 1 sequence


Name:  CBG_HUMAN        Length:  405

(Sequence)
Asn-Xaa-Ser/Thr sequons (including Asn-Pro-Ser/Thr) are shown in blue.
Asparagines predicted to be N-glycosylated are shown in red.
Note that not all sequons are predicted glycosylated.

MPLLLYTCLLWLPTSGLWTVQAMDPNAAYVNMSNHHRGLASANVDFAFSLYKHLVALSPKKNIFISPVSISMALAMLSLG      80
TCGHTRAQLLQGLGFNLTERSETEIHQGFQHLHQLFAKSDTSLEMTMGNALFLDGSLELLESFSADIKHYYESEVLAMNF     160
QDWATASRQINSYVKNKTQGKIVDLFSGLDSPAILVLVNYIFFKGTWTQPFDLASTREENFYVDETTVVKVPMMLQSSTI     240
SYLHDSELPCQLVQMNYVGNGTVFFILPDKGKMNTVIAALSRDTINRWSAGLTSSQVDLYIPKVTISGVYDLGDVLEEMG     320
IADLFTNQANFSRITQDAQLKSSKVVHKAVLQLNEEGVDTAGSTGVTLNLTSKPIILRFNQPFIIMIFDHFTWSSLFLAR     400
VMNPV

(Annotation line)
`N' represents a predicted N-glycosylation site.
`n' represents an Asn with a positive score,
but not occuring within an Asn-Xaa-Ser/Thr sequon

..............................N.................................................      80
...............N................................................................     160
................................................................................     240
...................N............................................................     320
................................................N...............................     400
.....


(Threshold=0.5)
----------------------------------------------------------------------
SeqName      Position  Potential   Jury    NGlyc
                                 agreement result
----------------------------------------------------------------------
CBG_HUMAN      31 NMSN   0.7166     (9/9)   ++  <-- Predicted as N-glycosylated (++)
CBG_HUMAN      96 NLTE   0.6356     (8/9)   +   <-- Predicted as N-glycosylated (+)
CBG_HUMAN     176 NKTQ   0.3941     (7/9)   -   <-- A negative site
CBG_HUMAN     260 NGTV   0.7400     (9/9)   ++
CBG_HUMAN     330 NFSR   0.4233     (7/9)   -      see below for
CBG_HUMAN     369 NLTS   0.6684     (9/9)   ++    more information
----------------------------------------------------------------------
```

Figure 14

```
Name:  Sequence        Length:  41
LSENNAIEFRSFSQNATNVSNNSNTSNDSNVSPFVLKRHQR
..............N..N.......................

(Threshold=0.5)
----------------------------------------------------------------------
SeqName      Position  Potential   Jury    N-Glyc
                                 agreement result
----------------------------------------------------------------------
Sequence       15 NATN   0.6224     (8/9)   +
Sequence       18 NVSN   0.6433     (9/9)   ++
Sequence       21 NNSN   0.4158     (8/9)   -
Sequence       24 NTSN   0.4158     (8/9)   -
Sequence       27 NDSN   0.3619     (8/9)   -
Sequence       30 NVSP   0.1149     (9/9)   ---
----------------------------------------------------------------------
```

Figure 15

CS01-FL-NA

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACACTCTTTGTGGAATTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATG
GCATCCCACCCTGTGTCTCTGCATGCTGTGGGAGTCTCATACTGGAAAGCCTCTGAAGGGGCTGAG
TATGATGACCAGACATCCCAGAGAGAGAAAGAGGATGACAAGGTGTTCCCTGGGGGATCTCACACC
TATGTGTGGCAAGTCCTCAAGGAGAATGGACCCATGGCATCTGACCCACTCTGCCTGACATACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCACTGCTGGTGTGC
AGGGAAGGATCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGATGCTGCC
TCTGCCAGGGCATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCAC
TCCATTTTCCTGGAGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCT
CCCATCACCTTCCTCACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTTCTGCCAC
ATCTCTTCCCACCAGCATGATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCAGATTTGATGATGACAACTCTCCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAA
CACCCCAAGACATGGGTGCACTACATTGCTGCTGAGGAAGAGGACTGGGACTATGCACCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGTCTCAGTACCTCAACAATGGCCCACAAAGAATTGGAAGA
AAGTACAAGAAAGTCAGATTCATGGCCTACACTGATGAAACCTTCAAGACAAGAGAAGCCATTCAG
CATGAGTCTGGCATTCTGGGACCACTCCTGTATGGGGAAGTGGGAGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCAGGAGACTGCCAAAAGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGA
TACTACTCCTCTTTTGTGAACATGGAGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGAGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGATCATGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAAC
CCTGCTGGGGTGCAACTGGAAGACCCTGAGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACTCTCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCACAAACTGACTTCCTTTCTGTCTTCTTCTCTGGATACACCTTCAAGCACAAGATGGTG
TATGAGGACACCCTGACACTCTTCCCATTCTCTGGGGAAACTGTGTTCATGAGCATGGAGAACCCT
GGACTGTGGATTCTGGGATGCCACAACTCTGACTTCAGAAACAGGGGAATGACTGCACTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACTCTTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATGCCATTGAGCCCAGAAGCTTCTCTCAGAATCCACCTGTCCTGAAGAGA
CACCAGAGAGAGATCACCAGGACAACCCTCCAGTCTGACCAGGAAGAGATTGACTATGATGACACC
ATTTCTGTGGAGATGAAGAAGGAGGACTTTGACATCTATGATGAGGACGAGAACCAGTCTCCAAGA
TCATTCCAGAAGAAGACAAGACACTACTTCATTGCTGCTGTGGAAAGACTGTGGGACTATGGCATG
TCTTCCTCTCCCCATGTCCTCAGGAACAGGGCACAGTCTGGCTCTGTGCCACAGTTCAAGAAAGTG
GTCTTCCAGGAGTTCACTGATGGCTCATTCACCCAGCCCCTGTACAGAGGGGAACTGAATGAGCAC

(Continued)

Figure 16A

CTGGGACTCCTGGGACCATACATCAGGGCTGAGGTGGAAGACAACATCATGGTGACATTCAGAAAC
CAGGCCTCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAGCTATGAGGAAGACCAGAGACAAGGG
GCTGAGCCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCAC
CACATGGCACCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCATACTTCTCTGATGTGGACCTG
GAGAAAGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCT
GCACATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAG
TCATGGTACTTCACTGAGAACATGGAGAGAAACTGCAGAGCACCATGCAACATTCAGATGGAAGAC
CCCACCTTCAAGGAGAACTACAGGTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGG
CTTGTCATGGCACAGGACCAGAGAATCAGATGGTACCTGCTTTCTATGGGATCCAATGAGAACATT
CACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAGGAATACAAGATGGCCCTG
TACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGGAGG
GTGGAATGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTCCTGGTCTACAGCAAC
AAGTGCCAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGC
CAGTATGGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCATCAATGCATGGTCA
ACCAAGGAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATTCATGGCATCAAG
ACACAGGGGGCAAGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCATGTACTCTCTG
GATGGCAAGAAGTGGCAGACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTTCTTTGGCAAT
GTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCTCCCATCATTGCCAGATACATCAGGCTG
CACCCCACCCACTACTCAATCAGATCAACCCTCAGGATGGAACTGATGGGATGTGACCTGAACTCC
TGCTCAATGCCCCTGGGAATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCATCCTCTTAC
TTCACCAACATGTTTGCCACCTGGTCACCATCAAAAGCCAGGCTGCACCTCCAGGGAAGAAGCAAT
GCCTGGAGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGACTTCCAGAAGACAATGAAA
GTCACTGGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTGAAGGAGTTCCTG
ATCTCTTCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAGGTGTTC
CAGGGCAACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGATAC
CTGAGAATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGTGAG
GCACAAGACCTGTACTGA (SEQ ID NO:13)

Figure 16B

CS08-FL-NA

ATGCAGATCGAACTGAGCACTTGCTTCTTCCTGTGTCTCCTGCGCTTTTGCTTCTCCGCCACAAGG
AGATACTATCTCGGTGCCGTGGAGCTCAGCTGGGACTACATGCAGAGCGACTTGGGTGAACTGCCT
GTGGACGCCAGGTTTCCACCCCGCGTGCCCAAGAGTTTCCCGTTCAACACCAGTGTCGTGTACAAG
AAAACCCTCTTCGTGGAATTCACCGACCACCTGTTCAACATCGCCAAACCGCGCCCTCCCTGGATG
GGGCTGCTCGGCCCGACGATCCAGGCTGAGGTCTATGACACGGTGGTGATTACCCTCAAGAACATG
GCTAGCCACCCGGTGAGCCTGCACGCCGTGGGCGTGTCCTATTGGAAAGCGTCCGAGGGTGCGGAG
TACGATGACCAGACTTCACAGCGGGAGAAGGAAGACGACAAAGTGTTCCCCGGGGGTTCCCACACC
TATGTCTGGCAGGTCCTGAAGGAGAATGGTCCTATGGCCTCCGACCCATTGTGCCTCACCTACTCT
TACCTAAGCCATGTGGATCTCGTCAAGGACCTGAACTCGGGGCTGATCGGCGCCCTGCTCGTGTGC
CGGGAGGGCTCACTGGCCAAGGAGAAGACCCAAACTCTGCACAAGTTCATCCTGCTGTTCGCGGTA
TTCGACGAGGGGAAGTCCTGGCACTCCGAGACCAAGAACAGCCTGATGCAGGACCGCGACGCAGCC
TCGGCCCGTGCGTGGCCAAAGATGCACACCGTGAACGGCTACGTTAACAGGAGCCTACCCGGCCTG
ATCGGCTGCCACCGCAAATCGGTCTACTGGCATGTGATCGGAATGGGCACAACGCCCGAGGTCCAC
AGTATCTTCCTCGAGGGCCACACTTTCCTGGTCCGGAATCACCGCCAGGCCAGCCTGGAGATCAGC
CCCATAACCTTTCTGACGGCGCAGACCTTACTCATGGATCTCGGCCAGTTCCTCCTGTTCTGCCAC
ATTTCGTCCCACCAGCACGATGGGATGGAAGCATATGTGAAAGTGGACTCCTGCCCCGAGGAACCC
CAGCTTAGGATGAAGAACAATGAGGAGGCCGAGGACTACGACGATGACCTTACCGATTCAGAAATG
GACGTAGTACGCTTTGACGACGACAACTCTCCATCCTTCATACAGATTCGCTCCGTCGCCAAGAAG
CACCCTAAGACTTGGGTGCACTACATCGCGGCCGAGGAGGAGGACTGGGATTATGCTCCCCTGGTG
CTGGCCCCCGACGACCGCAGCTACAAGAGCCAGTACCTGAATAACGGGCCCCAGCGCATCGGCCGG
AAGTACAAGAAAGTGCGGTTCATGGCTTACACGGACGAGACCTTCAAGACCCGGGAGGCTATCCAG
CATGAGAGCGGCATCTTGGGGCCCCTCCTGTACGGCGAAGTTGGAGACACACTGCTGATCATCTTC
AAGAACCAGGCGAGCAGGCCCTACAACATCTACCCCCACGGCATTACCGATGTCCGGCCGTTGTAC
AGCCGACGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTTCCGATCCTGCCGGGCGAGATCTTC
AAGTACAAGTGGACTGTGACCGTGGAGGATGGGCCGACCAAGAGCGATCCGCGCTGCCTGACCCGT
TACTACTCCAGCTTTGTCAATATGGAGCGCGACCTCGCTAGCGGCTTGATTGGCCCTCTGCTGATC
TGCTACAAGGAGTCCGTGGACCAGAGGGGGAATCAGATCATGAGTGACAAGAGGAACGTGATCCTG
TTCTCCGTGTTCGACGAAAACCGCAGCTGGTATCTCACCGAGAATATCCAGCGCTTCCTGCCCAAC
CCGGCCGGTGTGCAGCTGGAGGACCCCGAGTTTCAGGCCAGCAACATCATGCATTCTATCAACGGA
TATGTGTTTGATTCCCTGCAGCTCTCAGTGTGTCTGCACGAGGTCGCCTACTGGTATATCCTCAGC
ATTGGGGCACAGACCGACTTCCTGAGCGTGTTCTTCTCCGGGTATACCTTCAAGCACAAGATGGTG
TACGAGGATACCCTGACCCTGTTCCCCTTTAGCGGCGAAACCGTGTTTATGTCTATGGAGAACCCC
GGGCTCTGGATCCTTGGCTGCCATAACTCCGACTTCCGCAACCGCGGAATGACCGCGCTCCTGAAA
GTGTCGAGTTGTGACAAGAACACCGGCGACTATTACGAGGACAGTTACGAGGACATCTCTGCGTAC
CTCCTTAGCAAGAATAACGCCATCGAGCCAAGATCCTTCAGCCAGAACCCCCCAGTGCTGAAGAGG
CATCAGCGGGAGATCACCCGCACGACCCTGCAGTCGGATCAGGAGGAGATTGATTACGACGACACG
ATCAGTGTGGAGATGAAGAAGGAGGACTTCGACATCTACGACGAAGATGAAAACCAGTCCCCTCGG
TCCTTCCAAAAGAAGACCCGGCACTACTTCATCGCCGCTGTGGAACGCCTGTGGGACTATGGAATG

(Continued)

Figure 17A

TCTTCTAGCCCTCACGTTTTGAGGAACCGCGCCCAGTCGGGCAGCGTGCCCCAGTTCAAGAAAGTG
GTGTTCCAGGAGTTCACCGACGGCTCCTTCACCCAGCCACTTTACCGGGGCGAGCTCAATGAACAT
CTGGGCCTGCTGGGACCCTACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACATTCCGGAAT
CAGGCCAGCAGACCATACAGTTTCTACAGTTCACTCATCTCCTACGAGGAGGACCAGCGCCAGGGG
GCTGAACCCCGTAAGAACTTCGTGAAGCCAAACGAAACAAAGACCTACTTCTGGAAGGTCCAGCAC
CACATGGCACCTACCAAGGACGAGTTCGATTGCAAGGCCTGGGCCTACTTCTCCGACGTGGACCTG
GAGAAAGATGTGCACAGCGGCCTGATTGGCCCTCTGCTGGTGTGTCACACGAACACACTCAACCCT
GCACACGGGCGGCAGGTCACTGTGCAGGAATTCGCCCTGTTCTTTACCATCTTTGATGAGACGAAG
TCCTGGTATTTCACCGAAAACATGGAGAGGAACTGCCGCGCACCCTGCAACATCCAGATGGAAGAT
CCGACATTCAAGGAGAACTACCGGTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGC
CTCGTGATGGCCCAAGACCAGCGTATCCGCTGGTATCTGCTGTCGATGGGCTCCAACGAGAACATC
CATAGTATCCACTTCAGCGGGCATGTCTTCACGGTGAGGAAAAAGGAGGAGTACAAGATGGCACTG
TACAACCTCTATCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCTCCAAGGCCGGCATCTGGAGA
GTGGAATGCCTGATCGGCGAGCACCTCCACGCTGGGATGTCCACGCTGTTCCTCGTTTACAGCAAT
AAGTGCCAGACCCCTCTGGGCATGGCGAGCGGCCACATCCGCGACTTCCAGATTACAGCCAGCGGC
CAGTACGGTCAGTGGGCTCCAAAGCTGGCCCGTCTGCACTACTCCGGATCCATCAACGCCTGGTCC
ACCAAGGAACCGTTCTCCTGGATCAAAGTAGACCTGCTAGCCCCCATGATCATTCACGGCATCAAG
ACACAAGGCGCCCGACAGAAGTTCTCGAGCCTCTATATCTCCCAGTTCATCATCATGTATAGCCTG
GACGGAAAGAAGTGGCAGACTTACCGCGGAAACTCGACAGGGACCCTGATGGTATTCTTCGGTAAC
GTGGACAGCTCCGGAATCAAGCACAACATCTTCAACCCACCCATTATCGCCCGCTACATCCGCCTG
CACCCCACTCACTATAGCATTAGGTCCACCCTGCGAATGGAGCTCATGGGCTGTGACCTGAACAGC
TGTAGCATGCCCCTCGGCATGGAGTCTAAGGCGATCTCCGACGCACAGATAACGGCATCATCCTAC
TTTACCAACATGTTCGCTACCTGGTCCCCCTCCAAGGCCCGACTCCACCTGCAAGGGAGATCCAAC
GCCTGGCGGCCACAGGTCAACAATCCCAAGGAGTGGCTGCAAGTGGACTTTCAGAAAACTATGAAA
GTCACCGGAGTGACCACACAGGGAGTGAAGTCTCTGCTGACCAGCATGTACGTGAAGGAGTTCCTC
ATCTCCAGTTCGCAGGATGGCCACCAGTGGACGTTGTTCTTCCAAAACGGTAAAGTCAAAGTCTTC
CAAGGGAACCAGGACAGCTTTACACCCGTCGTGAACTCCCTGGACCCCCCGCTTCTCACTAGATAC
CTCCGCATCCACCCTCAGAGCTGGGTGCACCAGATTGCCCTGCGCATGGAGGTTCTGGGGTGTGAA
GCCCAGGACCTGTACTAA (SEQ ID NO:14)

Figure 17B

CS10-FL-NA

ATGCAGATTGAGCTCTCCACCTGCTTCTTTCTCTGCCTTCTTCGCTTCTGCTTTTCTGCCACACGC
AGGTACTATTTGGGAGCAGTGGAACTGAGCTGGGATTACATGCAGAGTGACCTTGGTGAACTTCCT
GTGGACGCTCGTTTTCCACCTAGAGTTCCCAAGTCCTTCCCCTTCAACACCTCAGTGGTCTACAAG
AAAACGCTGTTTGTGGAGTTCACTGACCACCTCTTCAACATTGCCAAACCAAGACCCCCTTGGATG
GGATTGCTGGGACCCACAATACAAGCAGAAGTCTACGACACGGTGGTGATTACCCTGAAGAACATG
GCGTCACACCCTGTTTCACTTCACGCTGTTGGGGTCAGTTATTGGAAAGCCTCAGAGGGTGCGGAA
TACGATGATCAAACCAGCCAGAGGGAGAAGGAAGATGACAAGGTCTTTCCTGGGGGGTAGCCATACC
TATGTTTGGCAGGTGCTGAAAGAGAATGGGCCTATGGCCTCTGATCCCTTGTGCCTCACATACTCT
TACCTGAGTCACGTCGACCTGGTGAAAGACCTGAATAGCGGTCTGATTGGTGCACTGCTTGTTTGT
AGAGAGGGGAGTTTGGCCAAGGAGAAAACTCAGACTCTCCACAAGTTTATCCTCCTGTTTGCTGTG
TTCGACGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAGGACAGAGATGCTGCA
TCTGCAAGGGCTTGGCCAAAAATGCACACAGTGAACGGCTATGTGAATCGATCACTGCCAGGACTG
ATAGGCTGTCATCGCAAGTCAGTGTATTGGCACGTTATCGGGATGGGAACAACTCCAGAAGTGCAC
AGCATCTTCCTTGAGGGCCACACTTTCCTGGTTCGGAATCATAGACAGGCCAGCCTTGAGATCAGC
CCAATCACCTTTCTGACTGCCCAAACCTTGCTGATGGATCTGGGACAGTTCCTCCTGTTTTGTCAC
ATCTCCTCCCACCAACATGACGGGATGGAGGCTTATGTGAAGGTCGATAGCTGTCCGGAGGAACCA
CAACTGAGGATGAAGAACAACGAAGAGGCAGAGGACTATGACGACGATCTGACTGACAGTGAAATG
GACGTGGTTCGGTTCGACGATGACAATTCTCCTTCATTTATCCAGATCCGTTCCGTGGCCAAGAAG
CACCCCAAGACTTGGGTTCATTACATCGCTGCTGAGGAGGAGGATTGGGACTACGCGCCCTTGGTG
TTGGCCCCAGACGATCGCTCATACAAGAGCCAGTACCTTAACAATGGTCCACAAAGGATCGGCCGG
AAGTACAAGAAGGTTAGATTTATGGCTTATACCGACGAGACTTTTAAAACTAGGGAAGCAATTCAG
CATGAAAGTGGCATTCTTGGACCCCTGCTGTATGGCGAGGTTGGCGACACCCTGCTGATTATCTTT
AAGAACCAGGCAAGCCGGCCCTACAACATCTACCCGCACGGCATAACCGATGTACGACCCCTGTAC
AGTCGCAGACTTCCTAAAGGGGTGAAACACCTGAAGGACTTCCCAATTCTGCCCGGGGAGATCTTC
AAGTATAAATGGACCGTGACGGTTGAGGATGGTCCCACAAAGTCCGATCCGAGATGCCTTACCCGA
TATTATTCCAGCTTCGTGAACATGGAAAGGGACCTGGCCAGCGGGCTGATTGGCCCACTGCTGATT
TGTTACAAGGAGTCTGTCGATCAAAGAGGAAACCAAATAATGAGCGACAAACGTAACGTCATCCTG
TTCAGCGTCTTTGATGAGAATAGAAGCTGGTACCTCACAGAAAATATTCAGCGGTTTCTGCCTAAC
CCCGCAGGCGTCCAGCTGGAAGATCCCGAGTTCCAAGCCTCAAACATCATGCATAGCATCAACGGA
TACGTATTCGATAGCCTGCAGCTGTCCGTCTGTCTCCATGAAGTGGCATATTGGTACATCCTGAGT
ATCGGGGCGCAGACCGACTTCCTGAGCGTGTTCTTTTCTGGATACACGTTCAAACACAAAATGGTC
TATGAAGATACCCTGACTCTGTTTCCATTCTCAGGAGAGACAGTCTTTATGAGTATGGAAAATCCT
GGACTGTGGATCCTGGGCTGTCACAATTCTGATTTTCGGAACAGAGGCATGACAGCCCTGCTTAAA
GTGAGCTCATGCGACAAGAACACCGGTGATTACTACGAAGATAGCTATGAGGACATCAGTGCGTAT
TTGCTCTCCAAGAACAACGCTATCGAGCCACGGTCTTTCAGTCAGAATCCTCCCGTTCTGAAGCGG
CATCAGCGCGAAATAACACGCACAACCCTTCAGTCAGACCAAGAGGAAATCGACTACGATGATACT
ATCTCTGTGGAGATGAAGAAGGAGGATTTCGACATTTACGACGAGGACGAGAATCAGTCCCCAAGG
AGCTTTCAGAAGAAAACAAGACACTATTTCATTGCCGCCGTGGAGCGACTGTGGGACTACGGCATG

(Continued)

Figure 18A

TCTAGCTCTCCGCATGTACTTAGAAATAGGGCACAAAGCGGATCCGTGCCTCAGTTTAAGAAAGTT
GTCTTTCAGGAGTTTACAGATGGCTCCTTCACCCAGCCCTTGTATCGCGGGGAACTCAATGAACAC
CTGGGCCTCCTGGGTCCTTATATTAGGGCCGAAGTCGAGGACAATATCATGGTGACCTTTAGGAAC
CAGGCATCTAGACCTTACTCTTTCTACTCCTCCCTGATATCCTATGAGGAGGACCAGCGGCAAGGC
GCTGAGCCTCGGAAGAACTTTGTGAAGCCAAATGAAACCAAAACATACTTTTGGAAAGTTCAGCAC
CACATGGCTCCCACGAAGGACGAATTTGACTGTAAAGCCTGGGCCTACTTCTCAGATGTAGATCTC
GAGAAAGACGTGCACTCAGGGCTCATTGGTCCCCTCCTGGTCTGTCATACTAATACCCTCAATCCA
GCACACGGACGTCAGGTAACCGTCCAGGAATTTGCCCTGTTCTTTACCATTTTCGATGAGACTAAA
TCCTGGTACTTTACCGAAAACATGGAGAGGAATTGCAGAGCCCCATGCAACATCCAGATGGAGGAC
CCTACCTTCAAAGAGAACTATCGCTTCCATGCCATTAACGGTTACATTATGGATACTCTCCCAGGA
CTTGTGATGGCACAGGATCAGCGGATAAGATGGTATCTGTTGAGCATGGGCTCCAACGAGAATATT
CACAGCATCCATTTCTCCGGTCACGTGTTTACAGTGAGAAAGAAAGAAGAGTACAAGATGGCTCTG
TATAATCTCTATCCAGGCGTATTCGAAACGGTGGAGATGTTGCCTAGCAAGGCCGGCATTTGGCGA
GTAGAATGCCTTATCGGGGAACATCTGCATGCCGGAATGAGCACGCTCTTCCTGGTGTATAGTAAC
AAGTGCCAGACTCCGCTGGGCATGGCATCTGGCCATATACGGGACTTTCAGATTACGGCTAGCGGG
CAGTATGGGCAGTGGGCACCCAAACTTGCGCGACTGCACTATTCAGGCTCTATCAATGCATGGTCC
ACCAAGGAACCCTTCTCTTGGATTAAGGTGGACCTTTTGGCGCCCATGATAATCCATGGGATCAAA
ACCCAGGGCGCTCGTCAGAAATTCTCATCACTCTACATCTCTCAGTTCATAATAATGTATTCACTG
GATGGGAAGAAATGGCAGACTTACAGAGGAAACAGCACCGGGACGCTGATGGTGTTCTTTGGCAAC
GTGGACAGCAGCGGCATCAAACACAACATCTTCAATCCTCCCATTATTGCCCGTTATATTAGACTG
CATCCCACTCACTACTCTATACGCAGCACACTTAGGATGGAGCTCATGGGATGCGACCTGAACAGT
TGTAGTATGCCCTTGGGGATGGAGTCCAAAGCTATAAGCGACGCACAAATTACAGCTAGCTCTTAC
TTTACGAATATGTTCGCCACGTGGAGCCCAAGCAAAGCCCGGCTGCATTTGCAGGGTCGGAGTAAT
GCTTGGCGCCCACAGGTGAATAACCCTAAGGAATGGTTGCAAGTAGATTTCCAGAAAACTATGAAG
GTAACCGGCGTCACTACACAGGGAGTCAAGTCCCTCTTGACCTCTATGTACGTCAAGGAGTTCCTG
ATTAGCAGCAGTCAGGATGGGCACCAATGGACACTGTTCTTCCAGAATGGGAAAGTTAAAGTATTT
CAGGGTAACCAGGACTCCTTTACACCTGTGGTGAATAGCCTCGACCCACCCCTGCTGACACGATAC
CTCCGCATCCACCCTCAGTCTTGGGTGCATCAAATTGCCCTGCGAATGGAGGTGTTGGGATGCGAA
GCTCAGGACCTCTACTGA (SEQ ID NO:15)

Figure 18B

CS11-FL-NA

ATGCAGATCGAACTCTCTACTTGCTTCTTCCTGTGCCTTCTGAGGTTCTGCTTCTCTGCCACTCGC
CGATATTACCTCGGGGCCGTGGAGTTGAGTTGGGACTACATGCAATCAGATCTGGGCGAACTCCCT
GTGGATGCCCGATTCCCACCGCGCGTGCCCAAGTCTTTCCCATTTAATACTTCTGTGGTGTACAAG
AAGACATTGTTTGTGGAGTTTACCGATCACCTGTTCAACATCGCCAAACCGCGGCCCCCATGGATG
GGTCTGCTTGGGCCCACCATTCAAGCGGAGGTCTATGATACAGTGGTGATAACGCTTAAGAACATG
GCGAGCCACCCAGTGTCTCTGCATGCCGTTGGTGTATCATATTGGAAGGCCAGCGAAGGAGCGGAG
TACGATGACCAGACCTCTCAGAGAGAGAAGGAAGACGATAAGGTTTTTCCTGGCGGAAGTCATACA
TATGTATGGCAGGTCCTGAAAGAGAATGGGCCGATGGCTTCTGACCCCCTTTGTCTTACCTATAGT
TATCTGAGCCACGTGGACCTGGTCAAGGACCTCAACAGTGGTCTGATTGGGGCTCTGCTTGTTTGT
AGAGAGGGTAGCTTGGCTAAGGAGAAAACCCAAACACTCCATAAGTTCATTTTGCTGTTCGCGGTG
TTCGACGAGGGAAAGAGTTGGCACAGCGAAACAAAGAATTCACTGATGCAAGACAGGGACGCCGCT
TCCGCAAGGGCTTGGCCTAAGATGCATACGGTGAATGGGTATGTGAACCGGAGCCTCCCGGGGCTG
ATCGGGTGCCATCGCAAGTCTGTTTACTGGCACGTCATTGGAATGGGGACAACGCCAGAGGTACAT
AGTATATTTCTTGAAGGCCACACGTTCCTCGTACGGAACCACCGACAGGCTTCCCTGGAGATAAGC
CCCATTACCTTTCTGACCGCTCAGACTCTGCTGATGGACCTTGGCCAGTTTCTCCTGTTCTGCCAT
ATTAGCAGCCACCAGCACGACGGTATGGAAGCATACGTGAAAGTCGATAGCTGTCCTGAGGAGCCT
CAGCTCAGAATGAAGAACAACGAGGAGGCCGAAGACTATGACGATGACCTTACAGATTCCGAGATG
GACGTGGTGCGCTTTGACGACGATAACAGTCCTAGTTTCATTCAAATCAGATCCGTAGCCAAAAAG
CATCCAAAGACATGGGTGCATTACATTGCAGCCGAAGAGGAGGATTGGGATTATGCGCCCCTTGTT
CTGGCTCCAGATGACAGGAGCTATAAGTCCCAGTACTTGAACAACGGGCCACAGCGAATCGGTAGA
AAATATAAGAAGGTAAGATTCATGGCCTACACTGACGAAACATTTAAAACCAGGGAAGCTATCCAA
CACGAATCTGGAATTCTCGGCCCTCTGCTCTACGGTGAGGTGGGGGACACCTTGCTGATCATTTTC
AAAAATCAGGCATCCAGGCCTTACAACATATACCCCCATGGCATCACCGATGTCCGCCCGCTGTAT
TCCAGAAGACTCCCCAAGGGAGTGAAACATCTGAAAGATTTTCCCATCCTGCCGGGGCGAGATCTTT
AAATACAAATGGACTGTGACTGTAGAGGACGGGCCTACAAAATCAGACCCACGGTGCCTGACAAGG
TATTACAGTAGCTTCGTCAACATGGAACGCGACCTCGCCAGCGGACTCATTGGCCCACTGTTGATC
TGTTACAAAGAGTCAGTGGATCAGAGGGGAAATCAGATCATGAGCGATAAGAGAAACGTTATCCTG
TTTAGTGTCTTCGACGAGAACCGGTCTTGGTACCTTACTGAGAACATCCAGAGGTTCCTGCCGAAT
CCGGCTGGCGTTCAGCTCGAGGACCCAGAGTTCCAGGCCAGTAATATAATGCACTCAATCAACGGT
TATGTGTTCGATAGCCTGCAGCTGAGCGTCTGCCTCCACGAGGTAGCCTATTGGTACATATTGTCC
ATCGGGGCTCAGACCGATTTTCTGTCCGTGTTCTTTAGCGGGTATACCTTTAAACATAAAATGGTC
TATGAAGACACCCTGACCCTGTTCCCATTCTCCGGTGAGACTGTGTTCATGTCCATGGAGAACCCA
GGGCTGTGGATCCTGGGGTGTCACAATAGTGACTTTAGGAATCGGGGAATGACGGCACTGCTGAAG
GTGAGTTCTTGCGATAAAAATACAGGAGATTACTATGAGGATAGTTACGAGGATATCAGTGCCTAT
CTGCTTTCAAAAAACAACGCAATTGAGCCCCGGTCTTTCTCACAAAACCCCCCGGTGCTGAAGCGC
CACCAGCGCGAAATTACCCGGACAACCTTGCAGTCCGACCAGGAGGAAATCGATTATGACGATACT
ATCAGTGTAGAAATGAAAAAGGAGGATTTTGATATTTACGACGAAGACGAGAACCAGTCTCCGCGA

(Continued)

Figure 19A

AGTTTTCAGAAGAAAACGCGACACTACTTTATAGCTGCCGTGGAACGACTCTGGGATTATGGCATG
TCCTCCAGCCCTCATGTCCTTAGGAATCGAGCGCAGAGTGGCTCTGTGCCTCAGTTCAAAAAGGTT
GTGTTCCAGGAATTCACCGACGGCTCATTTACCCAGCCGCTGTACAGAGGCGAACTCAACGAACAC
CTTGGGCTGCTTGGGCCATATATTCGAGCAGAGGTGGAAGATAATATCATGGTAACCTTTAGAAAC
CAGGCGTCAAGACCCTATTCCTTCTACAGTTCTCTGATCAGCTACGAGGAGGACCAAAGACAGGGA
GCTGAACCCAGGAAGAACTTTGTGAAACCTAATGAGACCAAGACCTACTTCTGGAAGGTCCAGCAC
CATATGGCCCCAACTAAAGATGAATTCGATTGCAAGGCCTGGGCTTATTTCAGCGACGTGGATCTC
GAAAAGGATGTGCACAGCGGGTTGATCGGACCGCTTTTGGTGTGCCACACAAATACCCTCAATCCT
GCCCACGGGCGGCAGGTCACAGTTCAAGAGTTTGCACTCTTCTTTACAATATTTGACGAGACAAAG
TCATGGTATTTTACAGAGAATATGGAGAGAAATTGTCGCGCACCTTGCAACATTCAGATGGAGGAC
CCCACATTTAAGGAGAATTACAGATTTCATGCTATCAATGGGTACATTATGGATACTCTGCCTGGT
CTGGTCATGGCCCAGGATCAGCGCATAAGGTGGTACTTGCTGAGCATGGGATCTAATGAGAATATA
CACAGCATTCACTTCAGTGGCCACGTTTTTACTGTTAGAAAGAAGGAGGAGTACAAAATGGCGCTC
TACAACCTTTACCCGGGTGTGTTTGAGACAGTGGAGATGCTGCCAAGCAAGGCAGGCATCTGGAGG
GTTGAGTGTCTTATTGGGGAGCATCTGCATGCTGGAATGTCCACCCTCTTTCTTGTGTACAGCAAT
AAGTGCCAGACACCGCTTGGCATGGCCAGCGGCCACATTAGGGACTTTCAGATAACTGCCAGTGGA
CAGTACGGCCAGTGGGCTCCCAAGCTTGCAAGACTCCACTACTCCGGAAGCATAAACGCATGGAGC
ACCAAGGAACCCTTCTCTTGGATTAAGGTGGACCTGCTGGCGCCAATGATCATTCACGGCATAAAA
ACCCAAGGGGCACGACAGAAATTTTCATCTTTGTATATTAGTCAGTTTATCATCATGTACAGCTTG
GATGGAAAGAAGTGGCAGACGTACAGGGGCAATTCTACAGGAACACTTATGGTGTTTTTTGGGAAT
GTCGATTCCAGCGGGATCAAACATAACATCTTCAATCCTCCTATTATCGCCCGATATATCCGCCTG
CACCCTACGCATTACTCCATCAGGTCCACATTGAGAATGGAACTGATGGGGTGCGACCTGAATAGT
TGTAGTATGCCACTGGGCATGGAGTCTAAAGCCATCAGCGATGCACAGATCACTGCCAGCTCTTAC
TTCACCAACATGTTTGCAACTTGGTCCCCCTCTAAAGCTCGCCTGCATCTGCAGGGACGCTCAAAT
GCATGGCGACCACAGGTGAACAATCCAAAAGAGTGGCTCCAGGTCGACTTTCAGAAGACAATGAAG
GTAACAGGAGTGACAACCCAGGGTGTAAAAAGCCTCCTTACGAGTATGTACGTTAAGGAGTTTCTG
ATTTCTAGCTCCCAGGACGGACACCAGTGGACTCTGTTCTTCCAGAACGGCAAAGTGAAGGTATTT
CAGGGAAACCAGGATTCTTTTACCCCGGTAGTGAATAGCCTGGATCCACCGTTGCTGACCCGCTAT
CTGAGAATTCATCCACAATCCTGGGTGCATCAGATTGCCCTCCGGATGGAAGTGCTCGGCTGTGAA
GCTCAGGATCTGTATTAG (SEQ ID NO:16)

Figure 19B

CS40-FL-NA

ATGCAAATAGAGCTCTCCACCTGCTTCTTTCTGTGCCTTTTGCGATTCTGCTTTAGTGCCACCAGA
AGATACTACCTGGGTGCAGTGGAACTGTCATGGGACTATATGCAAAGTGATCTCGGTGAGCTGCCT
GTGGACGCAAGATTTCCTCCTAGAGTGCCAAAATCTTTTCCATTCAACACCTCAGTCGTGTACAAA
AAGACTCTGTTTGTAGAATTCACGGATCACCTTTTCAACATCGCTAAGCCAAGGCCACCCTGGATG
GGTCTGCTAGGTCCTACCATCCAGGCTGAGGTTTATGATACAGTGGTCATTACACTTAAGAACATG
GCTTCCCATCCTGTCAGTCTTCATGCTGTTGGTGTATCCTACTGGAAAGCTTCTGAGGGAGCTGAA
TATGATGATCAGACCAGTCAAAGGGAGAAAGAAGATGATAAAGTCTTCCCTGGTGGAAGCCATACA
TATGTCTGGCAGGTCCTGAAAGAGAATGGTCCAATGGCCTCTGACCCACTGTGCCTTACCTACTCA
TATCTTTCTCATGTGGACCTGGTAAAAGACTTGAATTCAGGCCTCATTGGAGCCCTACTAGTATGT
AGAGAAGGGAGTCTGGCCAAGGAAAAGACACAGACCTTGCACAAATTTATACTACTTTTTGCTGTA
TTTGATGAAGGGAAAAGTTGGCACTCAGAAACAAAGAACTCCTTGATGCAGGATAGGGATGCTGCA
TCTGCTCGGGCCTGGCCTAAAATGCACACAGTCAATGGTTATGTAAACAGGTCTCTGCCAGGTCTG
ATTGGATGCCACAGGAAATCAGTCTATTGGCATGTGATTGGAATGGGCACCACTCCTGAAGTGCAC
TCAATATTCCTCGAAGGTCACACATTTCTTGTGAGGAACCATCGCCAGGCGTCCTTGGAAATCTCG
CCAATAACTTTCCTTACTGCTCAAACACTCTTGATGGACCTTGGACAGTTTCTACTGTTTTGTCAT
ATCTCTTCCCACCAACATGATGGCATGGAAGCTTATGTCAAAGTAGACAGCTGTCCAGAGGAACCC
CAACTACGAATGAAAAATAATGAAGAAGCGGAAGACTATGATGATGATCTTACTGATTCTGAAATG
GATGTGGTCAGGTTTGATGATGACAACTCTCCTTCCTTTATCCAAATTCGCTCAGTTGCCAAGAAG
CATCCTAAAACTTGGGTACATTACATTGCTGCTGAAGAGGAGGACTGGGACTATGCTCCCTTAGTC
CTCGCCCCCGATGACAGAAGTTATAAAAGTCAATATTTGAACAATGGCCCTCAGCGGATTGGTAGG
AAGTACAAAAAAGTCCGATTTATGGCATACACAGATGAAACCTTTAAGACTCGTGAAGCTATTCAG
CATGAATCAGGAATCTTGGGACCTTTACTTTATGGGGAAGTTGGAGACACACTGTTGATTATATTT
AAGAATCAAGCAAGCAGACCATATAACATCTACCCTCACGGAATCACTGATGTCCGTCCTTTGTAT
TCAAGGAGATTACCAAAAGGTGTAAAACATTTGAAGGATTTTCCAATTCTGCCAGGAGAAATATTC
AAATATAAATGGACAGTGACTGTAGAAGATGGGCCAACTAAATCAGATCCTCGGTGCCTGACCCGC
TATTACTCTAGTTTCGTTAATATGGAGAGAGATCTAGCTTCAGGACTCATTGGCCCTCTCCTCATC
TGCTACAAAGAATCTGTAGATCAAAGAGGAAACCAGATAATGTCAGACAAGAGGAATGTCATCCTG
TTTTCTGTATTTGATGAGAACCGAAGCTGGTACCTCACAGAGAATATACAACGCTTTCTCCCCAAT
CCAGCTGGAGTGCAGCTTGAGGATCCAGAGTTCCAAGCCTCCAACATCATGCACAGCATCAATGGC
TATGTTTTTGATAGTTTGCAGTTGTCAGTTTGTTTGCATGAGGTGGCATACTGGTACATTCTAAGC
ATTGGAGCACAGACTGACTTCCTTTCTGTCTTCTTCTCTGGATATACCTTCAAACACAAAATGGTC
TATGAAGACACACTCACCCTATTCCCATTCTCAGGAGAAACTGTCTTCATGTCGATGGAAAACCCA
GGTCTATGGATTCTGGGGTGCCACAACTCAGACTTTCGGAACAGAGGCATGACCGCCTTACTGAAG
GTTTCTAGTTGTGACAAGAACACTGGTGATTATTACGAGGACAGTTATGAAGATATTTCAGCATAC
TTGCTGAGTAAAAACAATGCCATTGAACCAAGAAGCTTCTCCCAGAATCCACCAGTCTTGAAACGC
CATCAACGGGAAATAACTCGTACTACTCTTCAGTCAGATCAAGAGGAAATTGACTATGATGATACC
ATATCAGTTGAAATGAAGAAGGAAGATTTTGACATTTATGATGAGGATGAAAATCAGAGCCCCCGC
AGCTTTCAAAAGAAAACACGACACTATTTTATTGCTGCAGTGGAGAGGCTCTGGGATTATGGGATG

(Continued)

Figure 20A

AGTAGCTCCCCACATGTTCTAAGAAACAGGGCTCAGAGTGGCAGTGTCCCTCAGTTCAAGAAAGTT
GTTTTCCAGGAATTTACTGATGGCTCCTTTACTCAGCCCTTATACCGTGGAGAACTAAATGAACAT
TTGGGACTCCTGGGGCCATATATAAGAGCAGAAGTTGAAGATAATATCATGGTAACTTTCAGAAAT
CAGGCCTCTCGTCCCTATTCCTTCTATTCTAGCCTTATTTCTTATGAGGAAGATCAGAGGCAAGGA
GCAGAACCTAGAAAAAACTTTGTCAAGCCTAATGAAACCAAAACTTACTTTTGGAAAGTGCAACAT
CATATGGCACCCACTAAAGATGAGTTTGACTGCAAAGCCTGGGCTTATTTCTCTGATGTTGACCTG
GAAAAAGATGTGCACTCAGGCCTGATTGGACCCCTTCTGGTCTGCCACACTAACACACTGAACCCT
GCTCATGGGAGACAAGTGACAGTACAGGAATTTGCTCTGTTTTTCACCATCTTTGATGAGACCAAA
AGCTGGTACTTCACTGAAAATATGGAAAGAAACTGCAGGGCTCCCTGCAATATCCAGATGGAAGAT
CCCACTTTTAAAGAGAATTATCGCTTCCATGCAATCAATGGCTACATAATGGATACACTACCTGGC
TTAGTAATGGCTCAGGATCAAAGGATTCGATGGTATCTGCTCAGCATGGGCAGCAATGAAAACATC
CATTCTATTCATTTCAGTGGACATGTGTTCACTGTACGAAAAAAAAGAGGAGTATAAAATGGCACTG
TACAATCTCTATCCAGGTGTTTTTGAGACAGTGGAAATGTTACCATCCAAAGCTGGAATTTGGCGG
GTGGAATGCCTTATTGGCGAGCATCTACATGCTGGGATGAGCACACTTTTTCTGGTGTACAGCAAT
AAGTGTCAGACTCCCCTGGGAATGGCTTCTGGACACATTAGAGATTTTCAGATTACAGCTTCAGGA
CAATATGGACAGTGGGCCCCAAAGCTGGCCAGACTTCATTATTCCGGATCAATCAATGCCTGGAGC
ACCAAGGAGCCCTTTTCTTGGATCAAGGTGGATCTGTTGGCACCAATGATTATTCACGGCATCAAG
ACCCAGGGTGCCCGTCAGAAGTTCTCCAGCCTCTACATCTCTCAGTTTATCATCATGTATAGTCTT
GATGGGAAGAAGTGGCAGACTTATCGAGGAAATTCCACTGGAACCTTAATGGTCTTCTTTGGCAAT
GTGGATTCATCTGGGATAAAACACAATATTTTTAACCCTCCAATTATTGCTCGATACATCCGTTTG
CACCCAACTCATTATAGCATTCGCAGCACTCTTCGCATGGAGTTGATGGGCTGTGATTTAAATAGT
TGCAGCATGCCATTGGGAATGGAGAGTAAAGCAATATCAGATGCACAGATTACTGCTTCATCCTAC
TTTACCAATATGTTTGCCACCTGGTCTCCTTCAAAAGCTCGACTTCACCTCCAAGGGAGGAGTAAT
GCCTGGAGACCTCAGGTGAATAATCCAAAAGAGTGGCTGCAAGTGGACTTCCAGAAGACAATGAAA
GTCACAGGAGTAACTACTCAGGGAGTAAAATCTCTGCTTACCAGCATGTATGTGAAGGAGTTCCTC
ATCTCCAGCAGTCAAGATGGCCATCAGTGGACTCTCTTTTTTCAGAATGGCAAAGTAAAGGTTTTT
CAGGGAAATCAAGACTCCTTCACACCTGTGGTGAACTCTCTAGACCCACCGTTACTGACTCGCTAC
CTTCGAATTCACCCCCAGAGTTGGGTGCACCAGATTGCCCTGAGGATGGAGGTTCTGGGCTGCGAG
GCACAGGACCTCTACTGA (SEQ ID NO:17)

Figure 20B

CH25-FL-NA

ATGCAGATCGAGCTGTCCACATGCTTTTTTCTGTGCCTGCTGCGGTTCTGCTTCAGCGCCACCCGG
CGGTACTACCTGGGCGCCGTGGAGCTGTCCTGGGACTACATGCAGAGCGACCTGGGCGAGCTGCCC
GTGGACGCCCGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAG
AAAACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCAGGCCCCCCTGGATG
GGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATG
GCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCTCCGAGGGCGCCGAG
TACGACGACCAGACCAGCCAGCGGGAGAAAGAGGACGACAAAGTCTTTCCTGGCGGCAGCCACACC
TACGTGTGGCAGGTCCTGAAAGAAAACGGCCCCATGGCCTCCGACCCCCTGTGCCTGACCTACAGC
TACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGGCTGATTGGGGCCCTGCTGGTCTGC
CGGGAGGGCAGCCTGGCCAAAGAGAAAACCCAGACCCTGCACAAGTTCATCCTGCTGTTCGCCGTG
TTCGACGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGCCTGATGCAGGACCGGGACGCCGCC
TCTGCCAGAGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGAAGCCTGCCCGGCCTG
ATTGGCTGCCACCGGAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACACCCGAGGTGCAC
AGCATCTTTCTGGAAGGGCACACCTTTCTGGTGCGGAACCACCGGCAGGCCAGCCTGGAAATCAGC
CCTATCACCTTCCTGACCGCCCAGACACTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTGCCAC
ATCAGCTCTCACCAGCACGACGGCATGGAAGCCTACGTGAAGGTGGACTCCTGCCCCGAGGAACCC
CAGCTGCGGATGAAGAACAACGAGGAAGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATG
GACGTGGTGCGGTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCAGAAGCGTGGCCAAGAAG
CACCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAAGAGGACTGGGACTACGCCCCCCTGGTG
CTGGCCCCCGACGACAGAAGCTACAAGAGCCAGTACCTGAACAATGGCCCCCAGCGGATCGGCCGG
AAGTACAAGAAAGTGCGGTTCATGGCCTACACCGACGAGACCTTCAAGACCCGGGAGGCCATCCAG
CACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGCGAAGTGGGCGACACACTGCTGATCATCTTC
AAGAACCAGGCCAGCCGGCCCTACAACATCTACCCCCACGGCATCACCGACGTGCGGCCCCTGTAC
AGCAGGCGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC
AAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCAGATGCCTGACCCGG
TACTACAGCAGCTTCGTGAACATGGAACGGGACCTGGCCTCCGGGCTGATCGGACCTCTGCTGATC
TGCTACAAAGAAAGCGTGGACCAGCGGGGCAACCAGATCATGAGCGACAAGCGGAACGTGATCCTG
TTCAGCGTGTTCGATGAGAACCGGTCCTGGTATCTGACCGAGAACATCCAGCGGTTTCTGCCCAAC
CCTGCCGGGGTGCAGCTGGAAGATCCCGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGC
TACGTGTTCGACAGCCTGCAGCTGTCCGTGTGTCTGCACGAGGTGGCCTACTGGTACATCCTGAGC
ATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGTG
TACGAGGACACCCTGACCCTGTTCCCTTTCAGCGGCGAGACCGTGTTCATGAGCATGGAAAACCCC
GGCCTGTGGATCCTGGGCTGCCACAACAGCGACTTCCGGAACCGGGGCATGACCGCCCTGCTGAAG
GTGTCCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGATATCAGCGCCTAC
CTGCTGTCCAAGAACAACGCCATCGAGCCCAGAAGCTTCAGCCAGAACCCCCCTGTGCTGAAGCGG
CACCAGAGAGAGATCACCCGGACCACCCTGCAGTCCGACCAGGAAGAGATCGATTACGACGACACC

(Continued)

Figure 21A

ATCAGCGTGGAGATGAAAAAAGAAGATTTCGACATCTACGACGAGGACGAGAACCAGAGCCCCCGG
TCCTTCCAGAAGAAAACCCGGCACTACTTTATCGCCGCCGTGGAGCGGCTGTGGGACTACGGCATG
AGCAGCAGCCCCCACGTGCTGCGGAACCGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAAGTG
GTGTTCCAGGAATTCACCGACGGCAGCTTCACCCAGCCCCTGTACCGGGGCGAGCTGAACGAGCAC
CTGGGGCTGCTGGGGCCCTACATCAGGGCCGAAGTGGAGGACAACATCATGGTGACCTTCCGGAAT
CAGGCCAGCAGACCCTACTCCTTCTACAGCAGCCTGATCAGCTACGAAGAGGACCAGCGGCAGGGC
GCTGAACCCCGGAAGAACTTCGTGAAGCCCAATGAGACCAAGACCTACTTCTGGAAAGTGCAGCAC
CACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTGGATCTG
GAAAAGGACGTGCACTCTGGACTGATTGGCCCTCTGCTGGTGTGCCACACCAACACCCTGAACCCC
GCCCACGGCCGGCAGGTGACCGTGCAGGAATTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAG
TCCTGGTACTTCACCGAGAATATGGAACGGAACTGCAGAGCCCCCTGCAACATCCAGATGGAAGAT
CCTACCTTCAAAGAGAACTACCGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCTGGC
CTGGTGATGGCCCAGGACCAGAGGATCCGGTGGTATCTGCTGTCCATGGGCAGCAACGAGAATATC
CACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGAGGAAGAAAGAAGAGTACAAGATGGCCCTG
TACAACCTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGG
GTGGAGTGTCTGATCGGCGAGCACCTGCATGCCGGGATGAGCACCCTGTTTCTGGTGTACAGCAAC
AAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCCGGGACTTCCAGATCACCGCCTCCGGC
CAGTACGGCCAGTGGGCCCCCAAGCTGGCCCGGCTGCACTACAGCGGCAGCATCAACGCCTGGTCC
ACCAAAGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCTATGATCATCCACGGCATTAAG
ACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTG
GACGGCAAGAAGTGGCAGACCTACCGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAAC
GTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCCGGTACATCCGGCTG
CACCCCACCCACTACAGCATCAGATCCACCCTGCGGATGGAACTGATGGGCTGCGACCTGAACTCC
TGCAGCATGCCTCTGGGCATGGAAAGCAAGGCCATCAGCGACGCCCAGATCACAGCCAGCAGCTAC
TTCACCAACATGTTCGCCACCTGGTCCCCCTCCAAGGCCAGGCTGCACCTGCAGGGCCGGTCCAAC
GCCTGGCGGCCTCAGGTGAACAACCCCAAAGAATGGCTGCAGGTGGACTTTCAGAAAACCATGAAG
GTGACCGGCGTGACCACCCAGGGCGTGAAAAGCCTGCTGACCAGCATGTACGTGAAAGAGTTTCTG
ATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTGTTCTTTCAGAACGGCAAGGTGAAAGTGTTC
CAGGGCAACCAGGACTCCTTCACCCCCGTGGTGAACTCCCTGGACCCCCCCCTGCTGACCCGCTAC
CTGCGGATCCACCCCCAGTCTTGGGTGCACCAGATCGCCCTGAGGATGGAAGTGCTGGGATGTGAG
GCCCAGGATCTGTACTGA (SEQ ID NO:18)

Figure 21B

FVIII-FL-AA

mqielstcff lcllrfcfsa trryylgave lswdymqsdl gelpvdarfp prvpksfpfn
tsvvykktlf veftdhlfni akprppwmgl lgptiqaevy dtvvitlknm ashpvslhav
gvsywkaseg aeyddqtsqr ekeddkvfpg gshtyvwqvl kengpmasdp lcltysylsh
vdlvkdlnsg ligallvcre gslakektqt lhkfillfav fdegkswhse tknslmqdrd
aasarawpkm htvngyvnrs lpgligchrk svywhvigmg ttpevhsifl eghtflvrnh
rqasleispi tfltaqtllm dlgqfllfch isshqhdgme ayvkvdscpe epqlrmknne
eaedydddlt dsemdvvrfd ddnspsfiqi rsvakkhpkt wvhyiaaeee dwdyaplvla
pddrsyksqy lnngpqrigr kykkvrfmay tdetfktrea iqhesgilgp llygevgdtl
liifknqasr pyniyphgit dvrplysrrl pkgvkhlkdf pilpgeifky kwtvtvedgp
tksdprcltr yyssfvnmer dlasgligpl licykesvdq rgnqimsdkr nvilfsvfde
nrswylteni qrflpnpagv qledpefqas nimhsingyv fdslqlsvcl hevaywyils
igaqtdflsv ffsgytfkhk mvyedtltlf pfsgetvfms menpglwilg chnsdfrnrg
mtallkvssc dkntgdyyed syedisayll sknnaieprs fsqnsrhpst rqkqfnatti
pendiektdp wfahrtpmpk iqnvsssdll millrqsptph glslsdlqea kyetfsddps
pgaidsnnsl semthfrpql hhsgdmvftp esglqlrlne klgttaatel kkldfkvsst
snnlistips dnlaaqtdnt sslgppsmpv hydsqldttl fgkkssplte sggplslsee
nndskllesg lmnsqesswg knvsstesgr lfkgkrahgp alltkdnalf kvsislltkn
ktsnnsatnr kthidgpsll ienspsvwqn ilesdtefkk vtplihdrml mdknatalrl
nhmsnkttss knmemvqqkk egpippdaqn pdmsffkmlf lpesarwiqr thgknslnsg
qgpspkqlvs lgpeksvegq nflseknkvv vgkgeftkdv glkemvfpss rnlfltnldn
lhennthnqe kkiqeeiekk etliqenvvl pqihtvtgtk nfmknlflls trqnvegsyd
gayapvlqdf rslndstnrt kkhtahfskk geeenleglg nqtkqiveky acttrispnt
sqqnfvtqrs kralkqfrlp leetelekri ivddtstqws knmkhltpst ltqidyneke
kgaitqspls dcltrshsip qanrsplpia kvssfpsirp iyltrvlfqd nsshlpaasy
rkkdsgvqes shflqgakkn nlslailtle mtgdqrevgs lgtsatnsvt ykkventvlp
kpdlpktsgk vellpkvhiy qkdlfptets ngspghldlv egsllqgteg aikwneanrp
gkvpflrvat essaktpskl ldplawdnhy gtqipkeewk sqekspekta fkkkdtilsl
nacesnhaia ainegqnkpe ievtwakqgr terlcsqnpp vlkrhqreit rttlqsdqee
idyddtisve mkkedfdiyd edenqsprsf qkktrhyfia averlwdygm sssphvlrnr
aqsgsvpqfk kvvfqeftdg sftqplyrge lnehlgllgp yiraevedni mvtfrnqasr
pysfyssiis yeedqrqgae prknfvkpne tktyfwkvqh hmaptkdefd ckawayfsdv
dlekdvhsgl igpllvchtn tlnpahgrqv tvqefalfft ifdetkswyf tenmerncra
pcniqmedpt fkenyrfhai ngyimdtlpg lvmaqdqrir wyllsmgsne nihsihfsgh
vftvrkkeey kmalynlypg vfetvemlps kagiwrvecl igehlhagms tlflvysnkc
qtplgmasgh irdfqitasg qygqwapkla rlhysgsina wstkepfswi kvdllapmii
hgiktqgarq kfsslyisqf iimysldgkk wqtyrgnstg tlmvffgnvd ssgikhnifn
ppiiaryirl hpthysirst lrmelmgcdl nscsmplgme skaisdaqit assyftnmfa
twspskarlh lqgrsnawrp qvnnpkewlq vdfqktmkvt gvttqgvksl ltsmyvkefl
isssqdghqw tlffqngkvk vfqgnqdsft pvvnsldppl ltrylrihpq swvhqialrm
evlgceaqdl y (SEQ ID NO:19)

Figure 22

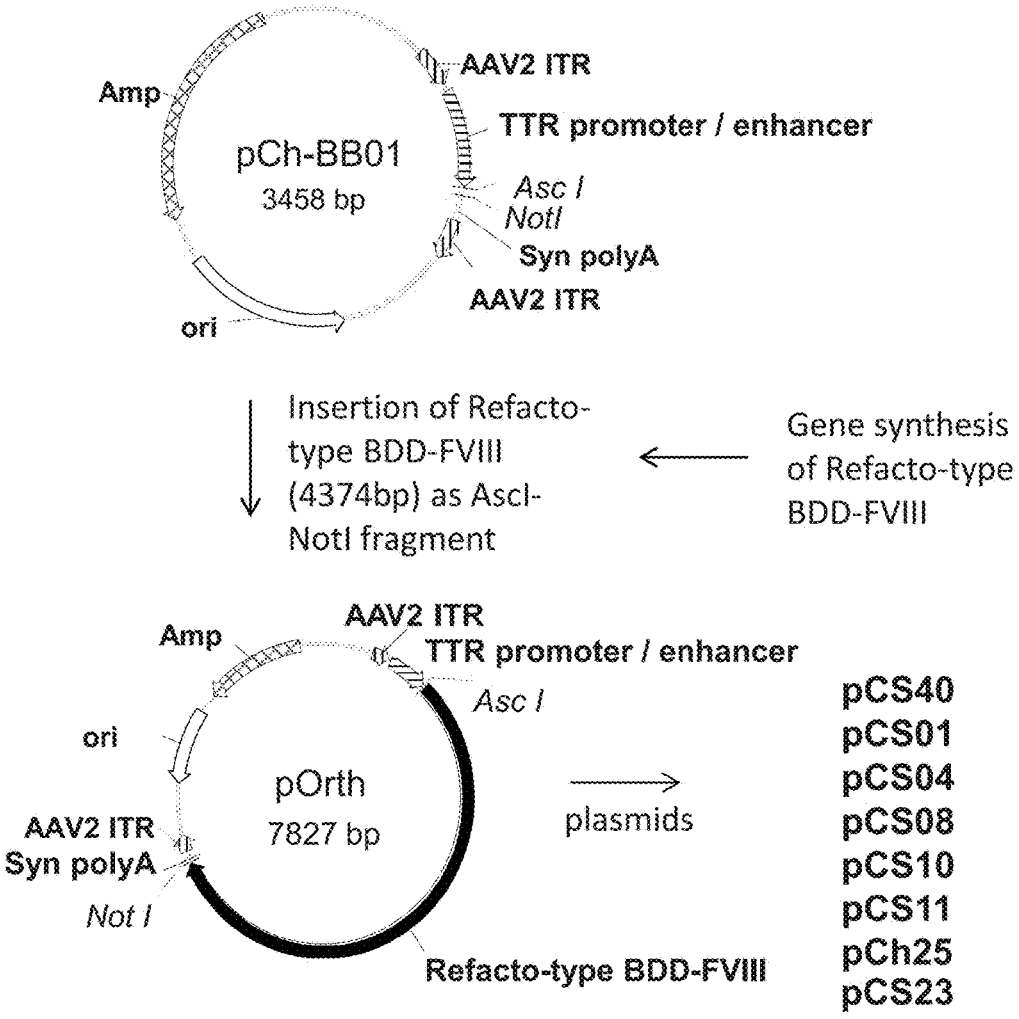

Amp
pCh-BB01
3458 bp
AAV2 ITR
TTR promoter / enhancer
Asc I
NotI
Syn polyA
AAV2 ITR
ori
Insertion of Refacto-type BDD-FVIII (4374bp) as AscI-NotI fragment
Gene synthesis of Refacto-type BDD-FVIII
Amp
AAV2 ITR
TTR promoter / enhancer
Asc I
ori
pOrth
7827 bp
AAV2 ITR
Syn polyA
Not I
Refacto-type BDD-FVIII
plasmids
pCS40
pCS01
pCS04
pCS08
pCS10
pCS11
pCh25
pCS23

Figure 23

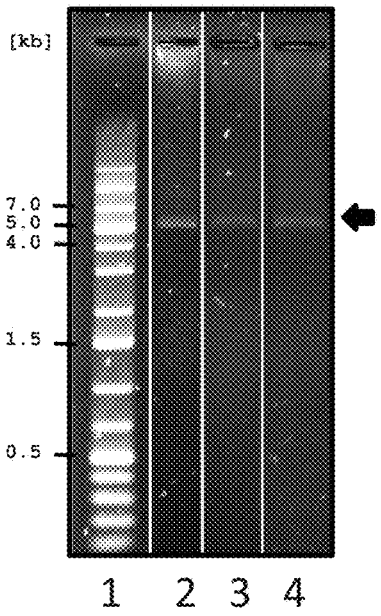


Figure 24

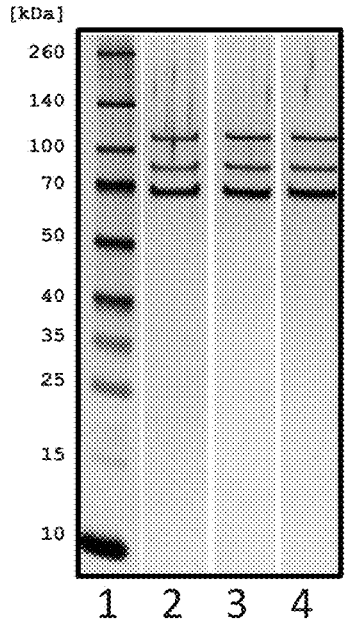


Figure 25

CS23-FL-NA

atgcagattgagctgagcacctgcttcttcctgtgcctgctgaggttctgcttctctgccaccagg
agatactacctgggcgccgtggagctgagctgggactacatgcagtctgacctgggcgagctgcct
gtggacgccaggttcccccccagagtgcccaagagcttcccctccaacacctcagtggtgtacaag
aagaccctgttcgtggagttcaccgaccacctgttcaacatcgccaagcccaggccccctggatg
ggcctgctgggccccaccatccaggccgaggtgtacgacaccgtggtgatcaccctgaagaacatg
gccagccaccccgtgagcctgcacgccgtgggcgtgagctactggaaggcctctgagggcgccgag
tatgacgaccagaccagccagagggagaaggaggacgacaaggtgttccccggcggcagccacacc
tacgtgtggcaggtgctgaaggagaacggccccatggccagcgacccctgtgcctgacctacagc
tacctgagccacgtggacctggtgaaggacctgaactctggcctgatcggcgccctgctggtgtgc
agggagggcagcctggccaaggagaagacccagaccctgcacaagttcatcctgctgttcgccgtg
ttcgatgagggcaagagctggcacagcgagaccaagaacagcctgatgcaggacagggatgccgcc
tctgccagggcctggcccaagatgcacaccgtgaacggctacgtgaacaggagcctgcccggcctg
atcggctgccacaggaagtctgtgtactggcacgtgatcggcatgggcaccacccccgaggtgcac
agcatcttcctggagggccacaccttcctggtgaggaaccacaggcaggccagcctggagatcagc
cccatcaccttcctgaccgcccagaccctgctgatggacctgggccagttcctgctgttctgccac
atcagcagccaccagcacgacggcatggaggcctacgtgaaggtggacagctgccccgaggagccc
cagctgaggatgaagaacaacgaggaggccgaggactatgatgatgacctgaccgactctgagatg
gacgtggtgaggtttgatgatgacaacagccccagcttcatccagatcaggtctgtggccaagaag
caccccaagacctgggtgcactacatcgccgccgaggaggaggactgggactacgcccccctggtg
ctggcccccgacgacaggagctacaagagccagtacctgaacaacggccccccagaggatcggcagg
aagtacaagaaggtcagattcatggcctacaccgacgagaccttcaagaccagggaggccatccag
cacgagtctggcatcctgggcccccctgctgtacggcgaggtgggcgacaccctgctgatcatcttc
aagaaccaggccagcaggccctacaacatctacccccacggcatcaccgatgtgaggcccctgtac
agcaggaggctgcccaagggcgtgaagcacctgaaggacttccccatcctgcccggcgagatcttc
aagtacaagtggaccgtgaccgtggaggatggccccaccaagtctgaccccaggtgcctgaccagg
tactacagcagcttcgtgaacatggagagggacctggcctctggcctgatcggcccctgctgatc
tgctacaaggagagcgtggaccagaggggcaaccagatcatgtctgacaagaggaacgtgatcctg
ttctctgtgttcgatgagaacaggagctggtatctgaccgagaacatccagaggttcctgcccaac
cccgccggcgtgcagctggaggaccccgagttccaggccagcaacatcatgcacagcatcaacggc
tacgtgttcgacagcctgcagctgtctgtgtgcctgcacgaggtggcctactggtacatcctgagc
atcggcgcccagaccgacttcctgtctgtgttcttctctggctacaccttcaagcacaagatggtg
tacgaggacaccctgaccctgttcccttcagcggcgagaccgtgttcatgagcatggagaacccc
ggcctgtggatcctgggctgccacaacagcgacttcaggaacaggggcatgaccgccctgctgaaa
gtcagcagctgcgacaagaacaccggcgactactacgaggacagctacgaggacatcagcgcctac
ctgctgagcaagaacaacgccatcgagcccaggagcttcagccagaaccccccccgtgctgaagagg
caccagagggagatcaccaggaccaccctgcagagcgaccaggaggagatcgactatgatgacacc

(Continued)

Figure 26A

atcagcgtggagatgaagaaggaggacttcgacatctacgacgaggacgagaaccagagccccagg
agcttccagaagaagaccaggcactacttcatcgccgccgtggagaggctgtgggactatggcatg
agcagcagccccacgtgctgaggaacagggcccagagcggcagcgtgccccagttcaagaaggtg
gtgttccaggagttcaccgacggcagcttcacccagcccctgtacagaggcgagctgaacgagcac
ctgggcctgctgggcccctacatcagggccgaggtggaggacaacatcatggtgaccttcaggaac
caggccagcaggccctacagcttctacagcagcctgatcagctacgaggaggaccagaggcagggc
gccgagcccaggaagaacttcgtgaagcccaacgagaccaagacctacttctggaaggtgcagcac
cacatggccccaccaaggacgagttcgactgcaaggcctgggcctacttctctgatgtggacctg
gagaaggacgtgcacagcggcctgatcggcccctgctggtgtgccacaccaacaccctgaacccc
gcccacggcaggcaggtgaccgtgcaggagttcgccctgttcttcaccatcttcgacgagaccaag
agctggtacttcaccgagaacatggagaggaactgcagggcccctgcaacatccagatggaggac
cccaccttcaaggagaactacaggttccacgccatcaacggctacatcatggacaccctgccggc
ctggtgatggcccaggaccagaggatcaggtggtatctgctgagcatgggcagcaacgagaacatc
cacagcatccacttcagcggccacgtgttcaccgtgaggaagaaggaggagtacaagatggccctg
tacaacctgtaccccggcgtgttcgagaccgtggagatgctgcccagcaaggccggcatctggagg
gtggagtgcctgatcggcgagcacctgcacgccggcatgagcaccctgttcctggtgtacagcaac
aagtgccagaccccctgggcatggccagcggccacatcagggacttccagatcaccgcctctggc
cagtacggccagtgggcccccaagctggccaggctgcactacagcggcagcatcaacgcctggagc
accaaggagcccttcagctggatcaaggtggacctgctggcccccatgatcatccacggcatcaag
acccagggcgccaggcagaagttcagcagcctgtacatcagccagttcatcatcatgtacagcctg
gacggcaagaagtggcagacctacaggggcaacagcaccggcaccctgatggtgttcttcggcaac
gtggacagcagcggcatcaagcacaacatcttcaacccccccatcatcgccaggtacatcaggctg
caccccacccactacagcatcaggagcaccctgcggatggaactgatgggctgcgacctgaacagc
tgcagcatgcccctgggcatggagagcaaggccatctctgacgcccagatcaccgccagcagctac
ttcaccaacatgttcgccacctggagccccagcaaggccaggctgcacctgcagggcaggagcaac
gcctggaggccccaggtgaacaaccccaaggagtggctgcaggtggacttccagaagaccatgaag
gtgaccggcgtgaccacccagggcgtgaagagcctgctgaccagcatgtacgtgaaggagttcctg
atcagcagcagccaggacggccaccagtggaccctgttcttccagaacggcaaagtgaaggtgttc
cagggcaaccaggacagcttcacCcccgtggtgaacagcctggacccccccctgctgaccaggtat
ctgaggatccacccccagagctgggtgcaccagatcgccctgagaatggaagtgctgggatgcgag
gcccaggacctgtactga (SEQ ID NO:20)

Figure 26B

CS23-FL-AA

MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDAR'FPPRVPKSFPFNTSVVYK
KTLFVEFTDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAVGVSYWKASEGAEY
DDQTSQREKEDDKVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSHVDLVKDLNSGLIGALLVCRE
GSLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGLIGC
HRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLFCHISSH
QHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKKHPKTW
VHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQHESGIL
GPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIFKYKWTVT
VEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVILFSVFDENR
SWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILSIGAQTDFLS
VFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLKVSSCDKNTGD
YYEDSYEDISAYLLSKNNAIEPRSFSQNPPVLKRHQREITRTTLQSDQEEIDYDDTISVEMKKEDFD
IYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSPHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQ
PLYRGELNEHLGLLGPYIRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNET
KTYFWKVQHHMAPTKDEFDCKAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALF
FTIFDETKSWYFTENMERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLS
MGSNENIHSIHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTL
FLVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVDLLAPMI
IHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSGIKHNIFNPPIIAR
YIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSYFTNMFATWSPSKARLHLQG
RSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFLISSSQDGHQWTLFFQNGKVK
VFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCEAQDLY (SEQ ID NO:21)

Figure 27

CS23-HC-NA

gcc
accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg
ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac
acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc
gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac
gacaccgtgg tgatcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg
ggcgtgagct actggaaggc ctctgagggc gccgagtatg acgaccagac cagccagagg
gagaaggagg acgacaaggt gttccccggc ggcagccaca cctacgtgtg gcaggtgctg
aaggagaacg gccccatggc cagcgacccc ctgtgcctga cctacagcta cctgagccac
gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag
ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg
ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat
gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc
ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc
accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac
aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg
gacctgggcc agttcctgct gttctgccac atcagcagcc accagcacga cggcatggag
gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag
gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat
gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc
tgggtgcact acatcgccgc cgaggaggag gactgggact acgccccccc ggtgctggcc
cccgacgaca ggagctacaa gagccagtac ctgaacaacg gccccccagag gatcggcagg
aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc
atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg
ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctacccccca cggcatcacc
gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc
cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc
accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg
gacctggcct ctggcctgat cggcccccctg ctgatctgct acaaggagag cgtggaccag
aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag
aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg
cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg
ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc
atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag
atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc
atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc
atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac
agctacgagg acatcagcgc ctacctgctg agcaagaaca acgccatcga gcccagg
(SEQ ID NO:22)

Figure 28

CS23-LC-NA

g agatcaccag gaccaccctg
cagagcgacc aggaggagat cgactatgat gacaccatca gcgtggagat gaagaaggag
gacttcgaca tctacgacga ggacgagaac cagagcccca ggagcttcca gaagaagacc
aggcactact tcatcgccgc cgtggagagg ctgtgggact atggcatgag cagcagcccc
cacgtgctga ggaacagggc ccagagcggc agcgtgcccc agttcaagaa ggtggtgttc
caggagttca ccgacggcag cttcacccag ccctgtaca gaggcgagct gaacgagcac
ctgggcctgc tgggccccta catcagggcc gaggtggagg acaacatcat ggtgaccttc
aggaaccagg ccagcaggcc ctacagcttc tacagcagcc tgatcagcta cgaggaggac
cagaggcagg gcgccgagcc caggaagaac ttcgtgaagc ccaacgagac caagacctac
ttctggaagg tgcagcacca catggccccc accaaggacg agttcgactg caaggcctgg
gcctacttct ctgatgtgga cctggagaag gacgtgcaca gcggcctgat cggccccctg
ctggtgtgcc acaccaacac cctgaacccc gcccacggca ggcaggtgac cgtgcaggag
ttcgccctgt tcttcaccat cttcgacgag accaagagct ggtacttcac cgagaacatg
gagaggaact gcagggcccc ctgcaacatc cagatggagg accccacctt caaggagaac
tacaggttcc acgccatcaa cggctacatc atggacaccc tgcccggcct ggtgatggcc
caggaccaga ggatcaggtg gtatctgctg agcatgggca gcaacgagaa catccacagc
atccacttca gcggccacgt gttcaccgtg aggaagaagg aggagtacaa gatggccctg
tacaacctgt accccggcgt gttcgagacc gtggagatgc tgcccagcaa ggccggcatc
tggagggtgg agtgcctgat cggcgagcac ctgcacgccg gcatgagcac cctgttcctg
gtgtacagca acaagtgcca gacccccctg ggcatggcca gcggccacat cagggacttc
cagatcaccg cctctggcca gtacggccag tgggcccccа agctggccag gctgcactac
agcggcagca tcaacgcctg gagcaccaag gagcccttca gctggatcaa ggtggacctg
ctggcccccа tgatcatcca cggcatcaag acccagggcg ccaggcagaa gttcagcagc
ctgtacatca gccagttcat catcatgtac agcctggacg gcaagaagtg gcagacctac
aggggcaaca gcaccggcac cctgatggtg ttcttcggca acgtggacag cagcggcatc
aagcacaaca tcttcaaccc ccccatcatc gccaggtaca tcaggctgca ccccacccac
tacagcatca ggagcaccct gcggatggaa ctgatgggct gcgacctgaa cagctgcagc
atgcccctgg gcatggagag caaggccatc tctgacgccc agatcaccgc cagcagctac
ttcaccaaca tgttcgccac ctggagcccc agcaaggcca ggctgcacct gcagggcagg
agcaacgcct ggaggcccca ggtgaacaac cccaaggagt ggctgcaggt ggacttccag
aagaccatga aggtgaccgg cgtgaccacc cagggcgtga agagcctgct gaccagcatg
tacgtgaagg agttcctgat cagcagcagc caggacggcc accagtggac cctgttcttc
cagaacggca aagtgaaggt gttccagggc aaccaggaca gcttcacccc cgtggtgaac
agcctggacc ccccccctgct gaccaggtat ctgaggatcc acccccagag ctgggtgcac
cagatcgccc tgagaatgga agtgctggga tgcgaggccc aggacctgta c
(SEQ ID NO:23)

Figure 29

CS01ml3-FL-NA

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACACTCTTTGTGGAATTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATG
GCATCCCACCCTGTGTCTCTGCATGCTGTGGGAGTCTCATACTGGAAAGCCTCTGAAGGGGCTGAG
TATGATGACCAGACATCCCAGAGAGAGAAAGAGGATGACAAGGTGTTCCCTGGGGGATCTCACACC
TATGTGTGGCAAGTCCTCAAGGAGAATGGACCCATGGCATCTGACCCACTCTGCCTGACATACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCACTGCTGGTGTGC
AGGGAAGGATCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGATGCTGCC
TCTGCCAGGGCATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCAC
TCCATTTTCCTGGAGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCT
CCCATCACCTTCCTCACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTCCTGCCAC
ATCTCTTCCCACCAGCATGATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCAGATTTGATGATGACAACTCTCCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAA
CACCCCAAGACATGGGTGCACTACATTGCTGCTGAGGAAGAGGACTGGGACTATGCACCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGTCTCAGTACCTCAACAATGGCCCACAAAGAATTGGAAGA
AAGTACAAGAAAGTCAGATTCATGGCCTACACTGATGAAACCTTCAAGACAAGAGAAGCCATTCAG
CATGAGTCTGGCATTCTGGGACCACTCCTGTATGGGGAAGTGGGAGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCAGGAGACTGCCAAAAGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGA
TACTACTCCTCTTTTGTGAACATGGAGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGAGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGATCATGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAAC
CCTGCTGGGGTGCAACTGGAAGACCCTGAGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACTCTCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCACAAACTGACTTCCTTTCTGTCTTCTTCTCTGGATACACCTTCAAGCACAAGATGGTG
TATGAGGACACCCTGACACTCTTCCCATTCTCTGGGGAAACTGTGTTCATGAGCATGGAGAACCCT
GGACTGTGGATTCTGGGATGCCACAACTCTGACTTCAGAAACAGGGGAATGACTGCACTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACTCTTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATACCACCTACGTGAACCGCTCCCTGTCTCAGAATCCACCTGTCCTGAAG
AGACACCAGAGAGAGATCACCAGGACAACCCTCCAGTCTGACCAGGAAGAGATTGACTATGATGAC
ACCATTTCTGTGGAGATGAAGAAGGAGGACTTTGACATCTATGATGAGGACGAGAACCAGTCTCCA
AGATCATTCCAGAAGAAGACAAGACACTACTTCATTGCTGCTGTGGAAAGACTGTGGGACTATGGC
ATGTCTTCCTCTCCCCATGTCCTCAGGAACAGGGCACAGTCTGGCTCTGTGCCACAGTTCAAGAAA

(Continued)

Figure 30A

GTGGTCTTCCAGGAGTTCACTGATGGCTCATTCACCCAGCCCCTGTACAGAGGGGAACTGAATGAG
CACCTGGGACTCCTGGGACCATACATCAGGGCTGAGGTGGAAGACAACATCATGGTGACATTCAGA
AACCAGGCCTCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAGCTATGAGGAAGACCAGAGACAA
GGGGCTGAGCCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAG
CACCACATGGCACCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCATACTTCTCTGATGTGGAC
CTGGAGAAAGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAAC
CCTGCACATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACC
AAGTCATGGTACTTCACTGAGAACATGGAGAGAAACTGCAGAGCACCATGCAACATTCAGATGGAA
GACCCCACCTTCAAGGAGAACTACAGGTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCT
GGGCTTGTCATGGCACAGGACCAGAGAATCAGATGGTACCTGCTTTCTATGGGATCCAATGAGAAC
ATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAGGAATACAAGATGGCC
CTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGG
AGGGTGGAATGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTCCTGGTCTACAGC
AACAAGTGCCAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCT
GGCCAGTATGGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCATCAATGCATGG
TCAACCAAGGAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATTCATGGCATC
AAGACACAGGGGGCAAGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCATGTACTCT
CTGGATGGCAAGAAGTGGCAGACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTTCTTTGGC
AATGTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCTCCCATCATTGCCAGATACATCAGG
CTGCACCCCACCCACTACTCAATCAGATCAACCCTCAGGATGGAACTGATGGGATGTGACCTGAAC
TCCTGCTCAATGCCCCTGGGAATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCATCCTCT
TACTTCACCAACATGTTTGCCACCTGGTCACCATCAAAAGCCAGGCTGCACCTCCAGGGAAGAAGC
AATGCCTGGAGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGACTTCCAGAAGACAATG
AAAGTCACTGGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTGAAGGAGTTC
CTGATCTCTTCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAGGTG
TTCCAGGGCAACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGA
TACCTGAGAATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGT
GAGGCACAAGACCTGTACTGA (SEQ ID NO:90)

Figure 30B

CS01m23-FL-NA

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACACTCTTTGTGGAATTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCGTCACCCTCAAGAACATG
GCATCCCACCCTGTGTCTCTGCATGCTGTGGGAGTCTCATACTGGAAATCCTCTGAAGGGGCTGAG
TATGATGACCAGACATCCCAGAGAGAGAAAGAGGATGACAAGGTGTTCCCTGGGAAGTCTCACACC
TATGTGTGGCAAGTCCTCAAGGAGAATGGACCCACTGCATCTGACCCACCCTGCCTGACATACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCACTGCTGGTGTGC
AGGGAAGGATCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGATGCTGCC
TCTGCCAGGGCATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCAC
TCCATTTTCCTGGAGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCT
CCCATCACCTTCCTCACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTTCTGCCAC
ATCTCTTCCCACCAGCATGATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCAGATTTGATGATGACAACTCTCCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAA
CACCCCAAGACATGGGTGCACTACATTGCTGCTGAGGAAGAGGACTGGGACTATGCACCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGTCTCAGTACCTCAACAATGGCCCACAAAGAATTGGAAGA
AAGTACAAGAAAGTCAGATTCATGGCCTACACTGATGAAACCTTCAAGACAAGAGAAGCCATTCAG
CATGAGTCTGGCATTCTGGGACCACTCCTGTATGGGGAAGTGGGAGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCAGGAGACTGCCAAAAGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGA
TACTACTCCTCTTTTGTGAACATGGAGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGAGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGATCATGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAAC
CCTGCTGGGGTGCAACTGGAAGACCCTGAGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACTCTCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCACAAACTGACTTCCTTTCTGTCTTCTTCTCTGGATACACCTTCAAGCACAAGATGGTG
TATGAGGACACCCTGACACTCTTCCCATTCTCTGGGGAAACTGTGTTCATGAGCATGGAGAACCCT
GGACTGTGGATTCTGGGATGCCACAACTCTGACTTCAGAAACAGGGGAATGACTGCACTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACTCTTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATACCACCTACGTGAACCGCTCCCTGTCTCAGAATCCACCTGTCCTGAAG
AGACACCAGAGAGAGATCACCAGGACAACCCTCCAGTCTGACCAGGAAGAGATTGACTATGATGAC
ACCATTTCTGTGGAGATGAAGAAGGAGGACTTTGACATCTATGATGAGGACGAGAACCAGTCTCCA
AGATCATTCCAGAAGAAGACAAGACACTACTTCATTGCTGCTGTGGAAAGACTGTGGGACTATGGC
ATGTCTTCCTCTCCCCATGTCCTCAGGAACAGGGCACAGTCTGGCTCTGTGCCACAGTTCAAGAAA

(Continued)

Figure 31A

GTGGTCTTCCAGGAGTTCACTGATGGCTCATTCACCCAGCCCCTGTACAGAGGGGAACTGAATGAG
CACCTGGGACTCCTGGGACCATACATCAGGGCTGAGGTGGAAGACAACATCATGGTGACATTCAGA
AACCAGGCCTCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAGCTATGAGGAAGACCAGAGACAA
GGGGCTGAGCCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAG
CACCACATGGCACCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCATACTTCTCTGATGTGGAC
CTGGAGAAAGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAAC
CCTGCACATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACC
AAGTCATGGTACTTCACTGAGAACATGGAGAGAAACTGCAGAGCACCATGCAACATTCAGATGGAA
GACCCCACCTTCAAGGAGAACTACAGGTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCT
GGGCTTGTCATGGCACAGGACCAGAGAATCAGATGGTACCTGCTTTCTATGGGATCCAATGAGAAC
ATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAGGAATACAAGATGGCC
CTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGG
AGGGTGGAATGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTCCTGGTCTACAGC
AACAAGTGCCAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCT
GGCCAGTATGGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCATCAATGCATGG
TCAACCAAGGAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATTCATGGCATC
AAGACACAGGGGGCAAGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCATGTACTCT
CTGGATGGCAAGAAGTGGCAGACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTTCTTTGGC
AATGTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCTCCCATCATTGCCAGATACATCAGG
CTGCACCCCACCCACTACTCAATCAGATCAACCCTCAGGATGGAACTGATGGGATGTGACCTGAAC
TCCTGCTCAATGCCCCTGGGAATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCATCCTCT
TACTTCACCAACATGTTTGCCACCTGGTCACCATCAAAAGCCAGGCTGCACCTCCAGGGAAGAAGC
AATGCCTGGAGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGACTTCCAGAAGACAATG
AAAGTCACTGGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTGAAGGAGTTC
CTGATCTCTTCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAGGTG
TTCCAGGGCAACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGA
TACCTGAGAATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGT
GAGGCACAAGACCTGTACTGA (SEQ ID NO:91)

Figure 31B

CS01m3-FL-NA

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACACTCTTTGTGGAATTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATG
GCATCCCACCCTGTGTCTCTGCATGCTGTGGGAGTCTCATACTGGAAAGCCTCTGAAGGGGCTGAG
TATGATGACCAGACATCCCAGAGAGAGAAAGAGGATGACAAGGTGTTCCCTGGGGGATCTCACACC
TATGTGTGGCAAGTCCTCAAGGAGAATGGACCCATGGCATCTGACCCACTCTGCCTGACATACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCACTGCTGGTGTGC
AGGGAAGGATCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGATGCTGCC
TCTGCCAGGGCATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCAC
TCCATTTTCCTGGAGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCT
CCCATCACCTTCCTCACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTTCTGCCAC
ATCTCTTCCCACCAGCATGATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCAGATTTGATGATGACAACTCTCCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAA
CACCCCAAGACATGGGTGCACTACATTGCTGCTGAGGAAGAGGACTGGGACTATGCACCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGTCTCAGTACCTCAACAATGGCCCACAAAGAATTGGAAGA
AAGTACAAGAAAGTCAGATTCATGGCCTACACTGATGAAACCTTCAAGACAAGAGAAGCCATTCAG
CATGAGTCTGGCATTCTGGGACCACTCCTGTATGGGGAAGTGGGAGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCAGGAGACTGCCAAAAGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGA
TACTACTCCTCTTTTGTGAACATGGAGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGAGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGATCATGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAAC
CCTGCTGGGGTGCAACTGGAAGACCCTGAGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACTCTCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCACAAACTGACTTCCTTTCTGTCTTCTTCTCTGGATACACCTTCAAGCACAAGATGGTG
TATGAGGACACCCTGACACTCTTCCCATTCTCTGGGGAAACTGTGTTCATGAGCATGGAGAACCCT
GGACTGTGGATTCTGGGATGCCACAACTCTGACTTCAGAAACAGGGGAATGACTGCACTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACTCTTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATACCACCTACGTGAACCGCTCCCTGTCTCAGAATCCACCTGTCCTGAAG
AGACACCAGAGAGAGATCACCAGGACAACCCTCCAGTCTGACCAGGAAGAGATTGACTATGATGAC
ACCATTTCTGTGGAGATGAAGAAGGAGGACTTTGACATCTATGATGAGGACGAGAACCAGTCTCCA
AGATCATTCCAGAAGAAGACAAGACACTACTTCATTGCTGCTGTGGAAAGACTGTGGGACTATGGC
ATGTCTTCCTCTCCCCATGTCCTCAGGAACAGGGCACAGTCTGGCTCTGTGCCACAGTTCAAGAAA

(Continued)

Figure 32A

GTGGTCTTCCAGGAGTTCACTGATGGCTCATTCACCCAGCCCCTGTACAGAGGGGAACTGAATGAG
CACCTGGGACTCCTGGGACCATACATCAGGGCTGAGGTGGAAGACAACATCATGGTGACATTCAGA
AACCAGGCCTCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAGCTATGAGGAAGACCAGAGACAA
GGGGCTGAGCCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAG
CACCACATGGCACCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCATACTTCTCTGATGTGGAC
CTGGAGAAAGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAAC
CCTGCACATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACC
AAGTCATGGTACTTCACTGAGAACATGGAGAGAAACTGCAGAGCACCATGCAACATTCAGATGGAA
GACCCCACCTTCAAGGAGAACTACAGGTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCT
GGGCTTGTCATGGCACAGGACCAGAGAATCAGATGGTACCTGCTTTCTATGGGATCCAATGAGAAC
ATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAGGAATACAAGATGGCC
CTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGG
AGGGTGGAATGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTCCTGGTCTACAGC
AACAAGTGCCAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCT
GGCCAGTATGGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCATCAATGCATGG
TCAACCAAGGAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATTCATGGCATC
AAGACACAGGGGGCAAGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCATGTACTCT
CTGGATGGCAAGAAGTGGCAGACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTTCTTTGGC
AATGTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCTCCCATCATTGCCAGATACATCAGG
CTGCACCCCACCCACTACTCAATCAGATCAACCCTCAGGATGGAACTGATGGGATGTGACCTGAAC
TCCTGCTCAATGCCCCTGGGAATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCATCCTCT
TACTTCACCAACATGTTTGCCACCTGGTCACCATCAAAAGCCAGGCTGCACCTCCAGGGAAGAAGC
AATGCCTGGAGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGACTTCCAGAAGACAATG
AAAGTCACTGGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTGAAGGAGTTC
CTGATCTCTTCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAGGTG
TTCCAGGGCAACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGA
TACCTGAGAATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGT
GAGGCACAAGACCTGTACTGA (SEQ ID NO:92)

Figure 32B

CS01m2-FL-NA

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACACTCTTTGTGGAATTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCGTCACCCTCAAGAACATG
GCATCCCACCCTGTGTCTCTGCATGCTGTGGGAGTCTCATACTGGAAATCCTCTGAAGGGGCTGAG
TATGATGACCAGACATCCCAGAGAGAGAAAGAGGATGACAAGGTGTTCCCTGGGAAGTCTCACACC
TATGTGTGGCAAGTCCTCAAGGAGAATGGACCCACTGCATCTGACCCACCCTGCCTGACATACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCACTGCTGGTGTGC
AGGGAAGGATCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGATGCTGCC
TCTGCCAGGGCATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCAC
TCCATTTTCCTGGAGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCT
CCCATCACCTTCCTCACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTTCTGCCAC
ATCTCTTCCCACCAGCATGATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCAGATTTGATGATGACAACTCTCCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAA
CACCCCAAGACATGGGTGCACTACATTGCTGCTGAGGAAGAGGACTGGGACTATGCACCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGTCTCAGTACCTCAACAATGGCCCACAAAGAATTGGAAGA
AAGTACAAGAAAGTCAGATTCATGGCCTACACTGATGAAACCTTCAAGACAAGAGAAGCCATTCAG
CATGAGTCTGGCATTCTGGGACCACTCCTGTATGGGGAAGTGGGAGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCAGGAGACTGCCAAAAGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGA
TACTACTCCTCTTTTGTGAACATGGAGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGAGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGATCATGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAAC
CCTGCTGGGGTGCAACTGGAAGACCCTGAGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACTCTCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCACAAACTGACTTCCTTTCTGTCTTCTTCTCTGGATACACCTTCAAGCACAAGATGGTG
TATGAGGACACCCTGACACTCTTCCCATTCTCTGGGGAAACTGTGTTCATGAGCATGGAGAACCCT
GGACTGTGGATTCTGGGATGCCACAACTCTGACTTCAGAAACAGGGGAATGACTGCACTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACTCTTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATGCCATTGAGCCCAGAAGCTTCTCTCAGAATCCACCTGTCCTGAAGAGA
CACCAGAGAGAGATCACCAGGACAACCCTCCAGTCTGACCAGGAAGAGATTGACTATGATGACACC
ATTTCTGTGGAGATGAAGAAGGAGGACTTTGACATCTATGATGAGGACGAGAACCAGTCTCCAAGA
TCATTCCAGAAGAAGACAAGACACTACTTCATTGCTGCTGTGGAAAGACTGTGGGACTATGGCATG
TCTTCCTCTCCCCATGTCCTCAGGAACAGGGCACAGTCTGGCTCTGTGCCACAGTTCAAGAAAGTG

(Continued)

Figure 33A

GTCTTCCAGGAGTTCACTGATGGCTCATTCACCCAGCCCCTGTACAGAGGGGAACTGAATGAGCAC
CTGGGACTCCTGGGACCATACATCAGGGCTGAGGTGGAAGACAACATCATGGTGACATTCAGAAAC
CAGGCCTCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAGCTATGAGGAAGACCAGAGACAAGGG
GCTGAGCCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCAC
CACATGGCACCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCATACTTCTCTGATGTGGACCTG
GAGAAAGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCT
GCACATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAG
TCATGGTACTTCACTGAGAACATGGAGAGAAACTGCAGAGCACCATGCAACATTCAGATGGAAGAC
CCCACCTTCAAGGAGAACTACAGGTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGG
CTTGTCATGGCACAGGACCAGAGAATCAGATGGTACCTGCTTTCTATGGGATCCAATGAGAACATT
CACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAGGAATACAAGATGGCCCTG
TACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGGAGG
GTGGAATGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTCCTGGTCTACAGCAAC
AAGTGCCAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGC
CAGTATGGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCATCAATGCATGGTCA
ACCAAGGAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATTCATGGCATCAAG
ACACAGGGGGCAAGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCATGTACTCTCTG
GATGGCAAGAAGTGGCAGACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTTCTTTGGCAAT
GTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCTCCCATCATTGCCAGATACATCAGGCTG
CACCCCACCCACTACTCAATCAGATCAACCCTCAGGATGGAACTGATGGGATGTGACCTGAACTCC
TGCTCAATGCCCCTGGGAATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCATCCTCTTAC
TTCACCAACATGTTTGCCACCTGGTCACCATCAAAAGCCAGGCTGCACCTCCAGGGAAGAAGCAAT
GCCTGGAGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGACTTCCAGAAGACAATGAAA
GTCACTGGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTGAAGGAGTTCCTG
ATCTCTTCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAGGTGTTC
CAGGGCAACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGATAC
CTGAGAATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGTGAG
GCACAAGACCTGTACTGA (SEQ ID NO:93)

Figure 33B

CS04m2-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGGCTGTGGAGCTTTCTTGGGACTACATGCAGTCTGACCTGGGGGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAATCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACCCTCTTTGTGGAGTTCACTGACCACCTGTTCAACATTGCCAAACCCAGGCCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCGTCACCCTCAAGAACATG
GCCTCCCACCCTGTGAGCCTGCATGCTGTGGGGGTCAGCTACTGGAAGTCCTCTGAGGGGGCTGAG
TATGATGACCAGACCTCCCAGAGGGAGAAGGAGGATGACAAAGTGTTCCCTGGGAAGAGCCACACC
TATGTGTGGCAGGTCCTCAAGGAGAATGGCCCCACTGCCTCTGACCCACCCTGCCTGACCTACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCCCTGCTGGTGTGC
AGGGAGGGCTCCCTGGCCAAAGAGAAGACCCAGACCCTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGAGCTGGCACTCTGAAACCAAGAACTCCCTGATGCAGGACAGGGATGCTGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGGAGCCTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAGGTGCAC
TCCATTTTCCTGGAGGGCCACACCTTCCTGGTCAGGAACCACAGACAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTCACTGCCCAGACCCTGCTGATGGACCTCGGACAGTTCCTGCTGTTCTGCCAC
ATCAGCTCCCACCAGCATGATGGCATGGAGGCCTATGTCAAGGTGGACAGCTGCCCTGAGGAGCCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCCGCTTTGATGATGACAACAGCCCATCCTTCATTCAGATCAGGTCTGTGGCCAAGAAA
CACCCCAAGACCTGGGTGCACTACATTGCTGCTGAGGAGGAGGACTGGGACTATGCCCCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGAGCCAGTACCTCAACAATGGCCCACAGAGGATTGGACGC
AAGTACAAGAAAGTCAGGTTCATGGCCTACACTGATGAAACCTTCAAGACCAGGGAGGCCATTCAG
CATGAGTCTGGCATCCTGGGCCCACTCCTGTATGGGGAGGTGGGGGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCCGCAGGCTGCCAAAGGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGGGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACCAAATCTGACCCCAGGTGCCTCACCAGA
TACTACTCCAGCTTTGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATTGGCCCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGGGGAAACCAGATCATGTCTGACAAGAGGAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGGAGCTGGTACCTGACTGAGAACATTCAGCGCTTCCTGCCCAAC
CCTGCTGGGGTGCAGCTGGAGGACCCTGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACAGCCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCCCAGACTGACTTCCTTTCTGTCTTCTTCTCTGGCTACACCTTCAAACACAAGATGGTG
TATGAGGACACCCTGACCCTCTTCCCATTCTCTGGGGAGACTGTGTTCATGAGCATGGAGAACCCT
GGCCTGTGGATTCTGGGATGCCACAACTCTGACTTCCGCAACAGGGGCATGACTGCCCTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACAGCTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATGCCATTGAGCCCAGGAGCTTCAGCCAGAATCCACCTGTCCTGAAACGC
CACCAGAGGGAGATCACCAGGACCACCCTCCAGTCTGACCAGGAGGAGATTGACTATGATGACACC
ATTTCTGTGGAGATGAAGAAAGAGGACTTTGACATCTATGACGAGGACGAGAACCAGAGCCCAAGG
AGCTTCCAGAAGAAGACCAGGCACTACTTCATTGCTGCTGTGGAGCGCCTGTGGGACTATGGCATG
AGCTCCAGCCCCCATGTCCTCAGGAACAGGGCCCAGTCTGGCTCTGTGCCACAGTTCAAGAAAGTG

(Continued)

Figure 34A

GTCTTCCAAGAGTTCACTGATGGCAGCTTCACCCAGCCCCTGTACAGAGGGGAGCTGAATGAGCAC
CTGGGACTCCTGGGCCCATACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACCTTCCGCAAC
CAGGCCTCCAGGCCCTACAGCTTCTACAGCTCCCTCATCAGCTATGAGGAGGACCAGAGGCAGGGG
GCTGAGCCACGCAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCAC
CACATGGCCCCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTG
GAGAAGGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCT
GCCCATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAG
AGCTGGTACTTCACTGAGAACATGGAGCGCAACTGCAGGGCCCCATGCAACATTCAGATGGAGGAC
CCCACCTTCAAAGAGAACTACCGCTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGG
CTTGTCATGGCCCAGGACCAGAGGATCAGGTGGTACCTGCTTTCTATGGGCTCCAATGAGAACATT
CACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGCGCAAGAAGGAGGAGTACAAGATGGCCCTG
TACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGGAGG
GTGGAGTGCCTCATTGGGGAGCACCTGCATGCTGGCATGAGCACCCTGTTCCTGGTCTACAGCAAC
AAGTGCCAGACCCCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGC
CAGTATGGCCAGTGGGCCCCCAAGCTGGCCAGGCTCCACTACTCTGGATCCATCAATGCCTGGAGC
ACCAAGGAGCCATTCAGCTGGATCAAAGTGGACCTGCTGGCCCCCATGATCATCCATGGCATCAAG
ACCCAGGGGGCCAGGCAGAAGTTCTCCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTG
GATGGCAAGAAATGGCAGACCTACAGAGGCAACTCCACTGGAACACTCATGGTCTTCTTTGGCAAT
GTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCCCCAATCATCGCCAGATACATCAGGCTG
CACCCCACCCACTACAGCATCCGCAGCACCCTCAGGATGGAGCTGATGGGCTGTGACCTGAACTCC
TGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCCTCCAGCTAC
TTCACCAACATGTTTGCCACCTGGAGCCCAAGCAAGGCCAGGCTGCACCTCCAGGGAAGGAGCAAT
GCCTGGAGGCCCCAGGTCAACAACCCAAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAG
GTCACTGGGGTGACCACCCAGGGGGTCAAGAGCCTGCTCACCAGCATGTATGTGAAGGAGTTCCTG
ATCAGCTCCAGCCAGGATGGCCACCAGTGGACCCTCTTCTTCCAGAATGGCAAGGTCAAGGTGTTC
CAGGGCAACCAGGACAGCTTCACCCCTGTGGTGAACAGCCTGGACCCCCCCCTCCTGACCAGATAC
CTGAGGATTCACCCCCAGAGCTGGGTCCACCAGATTGCCCTGAGGATGGAGGTCCTGGGATGTGAG
GCCCAGGACCTGTACTGA (SEQ ID NO:94)

Figure 34B

CS04m3-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAGCTTTCTTGGGACTACATGCAGTCTGACCTGGGGGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAATCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACCCTCTTTGTGGAGTTCACTGACCACCTGTTCAACATTGCCAAACCCAGGCCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATG
GCCTCCCACCCTGTGAGCCTGCATGCTGTGGGGGTCAGCTACTGGAAGGCCTCTGAGGGGGCTGAG
TATGATGACCAGACCTCCCAGAGGGAGAAGGAGGATGACAAAGTGTTCCCTGGGGGCAGCCACACC
TATGTGTGGCAGGTCCTCAAGGAGAATGGCCCCATGGCCTCTGACCCACTCTGCCTGACCTACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCCCTGCTGGTGTGC
AGGGAGGGCTCCCTGGCCAAAGAGAAGACCCAGACCCTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGAGCTGGCACTCTGAAACCAAGAACTCCCTGATGCAGGACAGGGATGCTGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGGAGCCTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAGGTGCAC
TCCATTTTCCTGGAGGGCCACACCTTCCTGGTCAGGAACCACAGACAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTCACTGCCCAGACCCTGCTGATGGACCTCGGACAGTTCCTGCTGTTCTGCCAC
ATCAGCTCCCACCAGCATGATGGCATGGAGGCCTATGTCAAGGTGGACAGCTGCCCTGAGGAGCCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCCGCTTTGATGATGACAACAGCCCATCCTTCATTCAGATCAGGTCTGTGGCCAAGAAA
CACCCCAAGACCTGGGTGCACTACATTGCTGCTGAGGAGGAGGACTGGGACTATGCCCCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGAGCCAGTACCTCAACAATGGCCCACAGAGGATTGGACGC
AAGTACAAGAAAGTCAGGTTCATGGCCTACACTGATGAAACCTTCAAGACCAGGGAGGCCATTCAG
CATGAGTCTGGCATCCTGGGCCCACTCCTGTATGGGGAGGTGGGGGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCCGCAGGCTGCCAAAGGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGGGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACCAAATCTGACCCCAGGTGCCTCACCAGA
TACTACTCCAGCTTTGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATTGGCCCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGGGGAAACCAGATCATGTCTGACAAGAGGAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGGAGCTGGTACCTGACTGAGAACATTCAGCGCTTCCTGCCCAAC
CCTGCTGGGGTGCAGCTGGAGGACCCTGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACAGCCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCCCAGACTGACTTCCTTTCTGTCTTCTTCTCTGGCTACACCTTCAAACACAAGATGGTG
TATGAGGACACCCTGACCCTCTTCCCATTCTCTGGGGAGACTGTGTTCATGAGCATGGAGAACCCT
GGCCTGTGGATTCTGGGATGCCACAACTCTGACTTCCGCAACAGGGGCATGACTGCCCTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACAGCTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATACCACCTACGTGAACCGCTCCCTGAGCCAGAATCCACCTGTCCTGAAA
CGCCACCAGAGGGAGATCACCAGGACCACCCTCCAGTCTGACCAGGAGGAGATTGACTATGATGAC
ACCATTTCTGTGGAGATGAAGAAAGAGGACTTTGACATCTATGACGAGGACGAGAACCAGAGCCCA
AGGAGCTTCCAGAAGAAGACCAGGCACTACTTCATTGCTGCTGTGGAGCGCCTGTGGGACTATGGC
ATGAGCTCCAGCCCCCATGTCCTCAGGAACAGGGCCCAGTCTGGCTCTGTGCCACAGTTCAAGAAA

(Continued)

Figure 35A

GTGGTCTTCCAAGAGTTCACTGATGGCAGCTTCACCCAGCCCCTGTACAGAGGGGAGCTGAATGAG
CACCTGGGACTCCTGGGCCCATACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACCTTCCGC
AACCAGGCCTCCAGGCCCTACAGCTTCTACAGCTCCCTCATCAGCTATGAGGAGGACCAGAGGCAG
GGGGCTGAGCCACGCAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAG
CACCACATGGCCCCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGAC
CTGGAGAAGGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAAC
CCTGCCCATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACC
AAGAGCTGGTACTTCACTGAGAACATGGAGCGCAACTGCAGGGCCCCATGCAACATTCAGATGGAG
GACCCCACCTTCAAAGAGAACTACCGCTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCT
GGGCTTGTCATGGCCCAGGACCAGAGGATCAGGTGGTACCTGCTTTCTATGGGCTCCAATGAGAAC
ATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGCGCAAGAAGGAGGAGTACAAGATGGCC
CTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGG
AGGGTGGAGTGCCTCATTGGGGAGCACCTGCATGCTGGCATGAGCACCCTGTTCCTGGTCTACAGC
AACAAGTGCCAGACCCCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCT
GGCCAGTATGGCCAGTGGGCCCCCAAGCTGGCCAGGCTCCACTACTCTGGATCCATCAATGCCTGG
AGCACCAAGGAGCCATTCAGCTGGATCAAAGTGGACCTGCTGGCCCCCATGATCATCCATGGCATC
AAGACCCAGGGGGCCAGGCAGAAGTTCTCCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGC
CTGGATGGCAAGAAATGGCAGACCTACAGAGGCAACTCCACTGGAACACTCATGGTCTTCTTTGGC
AATGTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCCCCAATCATCGCCAGATACATCAGG
CTGCACCCCACCCACTACAGCATCCGCAGCACCCTCAGGATGGAGCTGATGGGCTGTGACCTGAAC
TCCTGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCCTCCAGC
TACTTCACCAACATGTTTGCCACCTGGAGCCCAAGCAAGGCCAGGCTGCACCTCCAGGGAAGGAGC
AATGCCTGGAGGCCCCAGGTCAACAACCCAAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATG
AAGGTCACTGGGGTGACCACCCAGGGGGTCAAGAGCCTGCTCACCAGCATGTATGTGAAGGAGTTC
CTGATCAGCTCCAGCCAGGATGGCCACCAGTGGACCCTCTTCTTCCAGAATGGCAAGGTCAAGGTG
TTCCAGGGCAACCAGGACAGCTTCACCCCTGTGGTGAACAGCCTGGACCCCCCCCTCCTGACCAGA
TACCTGAGGATTCACCCCCAGAGCTGGGTCCACCAGATTGCCCTGAGGATGGAGGTCCTGGGATGT
GAGGCCCAGGACCTGTACTGA (SEQ ID NO:95)

Figure 35B

CS04m23-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAGCTTTCTTGGGACTACATGCAGTCTGACCTGGGGGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAATCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACCCTCTTTGTGGAGTTCACTGACCACCTGTTCAACATTGCCAAACCCAGGCCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCGTCACCCTCAAGAACATG
GCCTCCCACCCTGTGAGCCTGCATGCTGTGGGGGTCAGCTACTGGAAGTCCTCTGAGGGGGCTGAG
TATGATGACCAGACCTCCCAGAGGGAGAAGGAGGATGACAAAGTGTTCCCTGGGAAGAGCCACACC
TATGTGTGGCAGGTCCTCAAGGAGAATGGCCCCACTGCCTCTGACCCACCCTGCCTGACCTACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCCCTGCTGGTGTGC
AGGGAGGGCTCCCTGGCCAAAGAGAAGACCCAGACCCTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGAGCTGGCACTCTGAAACCAAGAACTCCCTGATGCAGGACAGGGATGCTGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGGAGCCTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAGGTGCAC
TCCATTTTCCTGGAGGGCCACACCTTCCTGGTCAGGAACCACAGACAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTCACTGCCCAGACCCTGCTGATGGACCTCGGACAGTTCCTGCTGTTCTGCCAC
ATCAGCTCCCACCAGCATGATGGCATGGAGGCCTATGTCAAGGTGGACAGCTGCCCTGAGGAGCCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCCGCTTTGATGATGACAACAGCCCATCCTTCATTCAGATCAGGTCTGTGGCCAAGAAA
CACCCCAAGACCTGGGTGCACTACATTGCTGCTGAGGAGGAGGACTGGGACTATGCCCCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGAGCCAGTACCTCAACAATGGCCCACAGAGGATTGGACGC
AAGTACAAGAAAGTCAGGTTCATGGCCTACACTGATGAAACCTTCAAGACCAGGGAGGCCATTCAG
CATGAGTCTGGCATCCTGGGCCCACTCCTGTATGGGGAGGTGGGGGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCCGCAGGCTGCCAAAGGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGGGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACCAAATCTGACCCCAGGTGCCTCACCAGA
TACTACTCCAGCTTTGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATTGGCCCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGGGGAAACCAGATCATGTCTGACAAGAGGAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGGAGCTGGTACCTGACTGAGAACATTCAGCGCTTCCTGCCCAAC
CCTGCTGGGGTGCAGCTGGAGGACCCTGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACAGCCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCCCAGACTGACTTCCTTTCTGTCTTCTTCTCTGGCTACACCTTCAAACACAAGATGGTG
TATGAGGACACCCTGACCCTCTTCCCATTCTCTGGGGAGACTGTGTTCATGAGCATGGAGAACCCT
GGCCTGTGGATTCTGGGATGCCACAACTCTGACTTCCGCAACAGGGGCATGACTGCCCTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACAGCTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATACCACCTACGTGAACCGCTCCCTGAGCCAGAATCCACCTGTCCTGAAA
CGCCACCAGAGGGAGATCACCAGGACCACCCTCCAGTCTGACCAGGAGGAGATTGACTATGATGAC
ACCATTTCTGTGGAGATGAAGAAAGAGGACTTTGACATCTATGACGAGGACGAGAACCAGAGCCCA
AGGAGCTTCCAGAAGAAGACCAGGCACTACTTCATTGCTGCTGTGGAGCGCCTGTGGGACTATGGC
ATGAGCTCCAGCCCCCATGTCCTCAGGAACAGGGCCCAGTCTGGCTCTGTGCCACAGTTCAAGAAA

(Continued)

Figure 36A

GTGGTCTTCCAAGAGTTCACTGATGGCAGCTTCACCCAGCCCCTGTACAGAGGGGAGCTGAATGAG
CACCTGGGACTCCTGGGCCCATACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACCTTCCGC
AACCAGGCCTCCAGGCCCTACAGCTTCTACAGCTCCCTCATCAGCTATGAGGAGGACCAGAGGCAG
GGGGCTGAGCCACGCAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAG
CACCACATGGCCCCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGAC
CTGGAGAAGGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAAC
CCTGCCCATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACC
AAGAGCTGGTACTTCACTGAGAACATGGAGCGCAACTGCAGGGCCCCATGCAACATTCAGATGGAG
GACCCCACCTTCAAAGAGAACTACCGCTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCT
GGGCTTGTCATGGCCCAGGACCAGAGGATCAGGTGGTACCTGCTTTCTATGGGCTCCAATGAGAAC
ATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGCGCAAGAAGGAGGAGTACAAGATGGCC
CTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGG
AGGGTGGAGTGCCTCATTGGGGAGCACCTGCATGCTGGCATGAGCACCCTGTTCCTGGTCTACAGC
AACAAGTGCCAGACCCCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCT
GGCCAGTATGGCCAGTGGGCCCCCAAGCTGGCCAGGCTCCACTACTCTGGATCCATCAATGCCTGG
AGCACCAAGGAGCCATTCAGCTGGATCAAAGTGGACCTGCTGGCCCCCATGATCATCCATGGCATC
AAGACCCAGGGGGCCAGGCAGAAGTTCTCCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGC
CTGGATGGCAAGAAATGGCAGACCTACAGAGGCAACTCCACTGGAACACTCATGGTCTTCTTTGGC
AATGTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCCCCAATCATCGCCAGATACATCAGG
CTGCACCCCACCCACTACAGCATCCGCAGCACCCTCAGGATGGAGCTGATGGGCTGTGACCTGAAC
TCCTGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCCTCCAGC
TACTTCACCAACATGTTTGCCACCTGGAGCCCAAGCAAGGCCAGGCTGCACCTCCAGGGAAGGAGC
AATGCCTGGAGGCCCCAGGTCAACAACCCAAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATG
AAGGTCACTGGGGTGACCACCCAGGGGGTCAAGAGCCTGCTCACCAGCATGTATGTGAAGGAGTTC
CTGATCAGCTCCAGCCAGGATGGCCACCAGTGGACCCTCTTCTTCCAGAATGGCAAGGTCAAGGTG
TTCCAGGGCAACCAGGACAGCTTCACCCCTGTGGTGAACAGCCTGGACCCCCCCCTCCTGACCAGA
TACCTGAGGATTCACCCCCAGAGCTGGGTCCACCAGATTGCCCTGAGGATGGAGGTCCTGGGATGT
GAGGCCCAGGACCTGTACTGA (SEQ ID NO:96)

Figure 36B

CS04m1-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGGCTGTGGAGCTTTCTTGGGACTACATGCAGTCTGACCTGGGGGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAATCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACCCTCTTTGTGGAGTTCACTGACCACCTGTTCAACATTGCCAAACCCAGGCCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATG
GCCTCCCACCCTGTGAGCCTGCATGCTGTGGGGGTCAGCTACTGGAAGGCCTCTGAGGGGGCTGAG
TATGATGACCAGACCTCCCAGAGGGAGAAGGAGGATGACAAAGTGTTCCCTGGGGGCAGCCACACC
TATGTGTGGCAGGTCCTCAAGGAGAATGGCCCCATGGCCTCTGACCCACTCTGCCTGACCTACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCCCTGCTGGTGTGC
AGGGAGGGCTCCCTGGCCAAAGAGAAGACCCAGACCCTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGAGCTGGCACTCTGAAACCAAGAACTCCCTGATGCAGGACAGGGATGCTGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGGAGCCTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAGGTGCAC
TCCATTTTCCTGGAGGGCCACACCTTCCTGGTCAGGAACCACAGACAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTCACTGCCCAGACCCTGCTGATGGACCTCGGACAGTTCCTGCTGTCCTGCCAC
ATCAGCTCCCACCAGCATGATGGCATGGAGGCCTATGTCAAGGTGGACAGCTGCCCTGAGGAGCCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCCGCTTTGATGATGACAACAGCCCATCCTTCATTCAGATCAGGTCTGTGGCCAAGAAA
CACCCCAAGACCTGGGTGCACTACATTGCTGCTGAGGAGGAGGACTGGGACTATGCCCCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGAGCCAGTACCTCAACAATGGCCCACAGAGGATTGGACGC
AAGTACAAGAAAGTCAGGTTCATGGCCTACACTGATGAAACCTTCAAGACCAGGGAGGCCATTCAG
CATGAGTCTGGCATCCTGGGCCCACTCCTGTATGGGGAGGTGGGGGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCCGCAGGCTGCCAAAGGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGGGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACCAAATCTGACCCCAGGTGCCTCACCAGA
TACTACTCCAGCTTTGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATTGGCCCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGGGGAAACCAGATCATGTCTGACAAGAGGAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGGAGCTGGTACCTGACTGAGAACATTCAGCGCTTCCTGCCCAAC
CCTGCTGGGGTGCAGCTGGAGGACCCTGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACAGCCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCCCAGACTGACTTCCTTTCTGTCTTCTTCTCTGGCTACACCTTCAAACACAAGATGGTG
TATGAGGACACCCTGACCCTCTTCCCATTCTCTGGGGAGACTGTGTTCATGAGCATGGAGAACCCT
GGCCTGTGGATTCTGGGATGCCACAACTCTGACTTCCGCAACAGGGGCATGACTGCCCTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACAGCTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATGCCATTGAGCCCAGGAGCTTCAGCCAGAATCCACCTGTCCTGAAACGC
CACCAGAGGGAGATCACCAGGACCACCCTCCAGTCTGACCAGGAGGAGATTGACTATGATGACACC
ATTTCTGTGGAGATGAAGAAAGAGGACTTTGACATCTATGACGAGGACGAGAACCAGAGCCCAAGG
AGCTTCCAGAAGAAGACCAGGCACTACTTCATTGCTGCTGTGGAGCGCCTGTGGGACTATGGCATG
AGCTCCAGCCCCCATGTCCTCAGGAACAGGGCCCAGTCTGGCTCTGTGCCACAGTTCAAGAAAGTG

(Continued)

Figure 37A

GTCTTCCAAGAGTTCACTGATGGCAGCTTCACCCAGCCCCTGTACAGAGGGGAGCTGAATGAGCAC
CTGGGACTCCTGGGCCCATACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACCTTCCGCAAC
CAGGCCTCCAGGCCCTACAGCTTCTACAGCTCCCTCATCAGCTATGAGGAGGACCAGAGGCAGGGG
GCTGAGCCACGCAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCAC
CACATGGCCCCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTG
GAGAAGGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCT
GCCCATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAG
AGCTGGTACTTCACTGAGAACATGGAGCGCAACTGCAGGGCCCCATGCAACATTCAGATGGAGGAC
CCCACCTTCAAAGAGAACTACCGCTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGG
CTTGTCATGGCCCAGGACCAGAGGATCAGGTGGTACCTGCTTTCTATGGGCTCCAATGAGAACATT
CACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGCGCAAGAAGGAGGAGTACAAGATGGCCCTG
TACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGGAGG
GTGGAGTGCCTCATTGGGGAGCACCTGCATGCTGGCATGAGCACCCTGTTCCTGGTCTACAGCAAC
AAGTGCCAGACCCCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGC
CAGTATGGCCAGTGGGCCCCCAAGCTGGCCAGGCTCCACTACTCTGGATCCATCAATGCCTGGAGC
ACCAAGGAGCCATTCAGCTGGATCAAAGTGGACCTGCTGGCCCCCATGATCATCCATGGCATCAAG
ACCCAGGGGGCCAGGCAGAAGTTCTCCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTG
GATGGCAAGAAATGGCAGACCTACAGAGGCAACTCCACTGGAACACTCATGGTCTTCTTTGGCAAT
GTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCCCCAATCATCGCCAGATACATCAGGCTG
CACCCCACCCACTACAGCATCCGCAGCACCCTCAGGATGGAGCTGATGGGCTGTGACCTGAACTCC
TGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCCTCCAGCTAC
TTCACCAACATGTTTGCCACCTGGAGCCCAAGCAAGGCCAGGCTGCACCTCCAGGGAAGGAGCAAT
GCCTGGAGGCCCCAGGTCAACAACCCAAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAG
GTCACTGGGGTGACCACCCAGGGGGTCAAGAGCCTGCTCACCAGCATGTATGTGAAGGAGTTCCTG
ATCAGCTCCAGCCAGGATGGCCACCAGTGGACCCTCTTCTTCCAGAATGGCAAGGTCAAGGTGTTC
CAGGGCAACCAGGACAGCTTCACCCCTGTGGTGAACAGCCTGGACCCCCCCCTCCTGACCAGATAC
CTGAGGATTCACCCCCAGAGCTGGGTCCACCAGATTGCCCTGAGGATGGAGGTCCTGGGATGTGAG
GCCCAGGACCTGTACTGA (SEQ ID NO:97)

Figure 37B

CS04m13-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAGCTTTCTTGGGACTACATGCAGTCTGACCTGGGGGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAATCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACCCTCTTTGTGGAGTTCACTGACCACCTGTTCAACATTGCCAAACCCAGGCCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATG
GCCTCCCACCCTGTGAGCCTGCATGCTGTGGGGGTCAGCTACTGGAAGGCCTCTGAGGGGGCTGAG
TATGATGACCAGACCTCCCAGAGGGAGAAGGAGGATGACAAAGTGTTCCCTGGGGGCAGCCACACC
TATGTGTGGCAGGTCCTCAAGGAGAATGGCCCCATGGCCTCTGACCCACTCTGCCTGACCTACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCCCTGCTGGTGTGC
AGGGAGGGCTCCCTGGCCAAAGAGAAGACCCAGACCCTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGAGCTGGCACTCTGAAACCAAGAACTCCCTGATGCAGGACAGGGATGCTGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGGAGCCTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAGGTGCAC
TCCATTTTCCTGGAGGGCCACACCTTCCTGGTCAGGAACCACAGACAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTCACTGCCCAGACCCTGCTGATGGACCTCGGACAGTTCCTGCTGTCCTGCCAC
ATCAGCTCCCACCAGCATGATGGCATGGAGGCCTATGTCAAGGTGGACAGCTGCCCTGAGGAGCCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCCGCTTTGATGATGACAACAGCCCATCCTTCATTCAGATCAGGTCTGTGGCCAAGAAA
CACCCCAAGACCTGGGTGCACTACATTGCTGCTGAGGAGGAGGACTGGGACTATGCCCCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGAGCCAGTACCTCAACAATGGCCCACAGAGGATTGGACGC
AAGTACAAGAAAGTCAGGTTCATGGCCTACACTGATGAAACCTTCAAGACCAGGGAGGCCATTCAG
CATGAGTCTGGCATCCTGGGCCCACTCCTGTATGGGGAGGTGGGGGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCCGCAGGCTGCCAAAGGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGGGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACCAAATCTGACCCCAGGTGCCTCACCAGA
TACTACTCCAGCTTTGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATTGGCCCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGGGGAAACCAGATCATGTCTGACAAGAGGAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGGAGCTGGTACCTGACTGAGAACATTCAGCGCTTCCTGCCCAAC
CCTGCTGGGGTGCAGCTGGAGGACCCTGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACAGCCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCCCAGACTGACTTCCTTTCTGTCTTCTTCTCTGGCTACACCTTCAAACACAAGATGGTG
TATGAGGACACCCTGACCCTCTTCCCATTCTCTGGGGAGACTGTGTTCATGAGCATGGAGAACCCT
GGCCTGTGGATTCTGGGATGCCACAACTCTGACTTCCGCAACAGGGGCATGACTGCCCTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACAGCTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATACCACCTACGTGAACCGCTCCCTGAGCCAGAATCCACCTGTCCTGAAA
CGCCACCAGAGGGAGATCACCAGGACCACCCTCCAGTCTGACCAGGAGGAGATTGACTATGATGAC
ACCATTTCTGTGGAGATGAAGAAAGAGGACTTTGACATCTATGACGAGGACGAGAACCAGAGCCCA
AGGAGCTTCCAGAAGAAGACCAGGCACTACTTCATTGCTGCTGTGGAGCGCCTGTGGGACTATGGC
ATGAGCTCCAGCCCCCATGTCCTCAGGAACAGGGCCCAGTCTGGCTCTGTGCCACAGTTCAAGAAA

(Continued)

Figure 38A

GTGGTCTTCCAAGAGTTCACTGATGGCAGCTTCACCCAGCCCCTGTACAGAGGGGAGCTGAATGAG
CACCTGGGACTCCTGGGCCCATACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACCTTCCGC
AACCAGGCCTCCAGGCCCTACAGCTTCTACAGCTCCCTCATCAGCTATGAGGAGGACCAGAGGCAG
GGGGCTGAGCCACGCAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAG
CACCACATGGCCCCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGAC
CTGGAGAAGGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAAC
CCTGCCCATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACC
AAGAGCTGGTACTTCACTGAGAACATGGAGCGCAACTGCAGGGCCCCATGCAACATTCAGATGGAG
GACCCCACCTTCAAAGAGAACTACCGCTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCT
GGGCTTGTCATGGCCCAGGACCAGAGGATCAGGTGGTACCTGCTTTCTATGGGCTCCAATGAGAAC
ATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGCGCAAGAAGGAGGAGTACAAGATGGCC
CTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGG
AGGGTGGAGTGCCTCATTGGGGAGCACCTGCATGCTGGCATGAGCACCCTGTTCCTGGTCTACAGC
AACAAGTGCCAGACCCCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCT
GGCCAGTATGGCCAGTGGGCCCCCAAGCTGGCCAGGCTCCACTACTCTGGATCCATCAATGCCTGG
AGCACCAAGGAGCCATTCAGCTGGATCAAAGTGGACCTGCTGGCCCCCATGATCATCCATGGCATC
AAGACCCAGGGGGCCAGGCAGAAGTTCTCCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGC
CTGGATGGCAAGAAATGGCAGACCTACAGAGGCAACTCCACTGGAACACTCATGGTCTTCTTTGGC
AATGTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCCCCAATCATCGCCAGATACATCAGG
CTGCACCCCACCCACTACAGCATCCGCAGCACCCTCAGGATGGAGCTGATGGGCTGTGACCTGAAC
TCCTGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCCTCCAGC
TACTTCACCAACATGTTTGCCACCTGGAGCCCAAGCAAGGCCAGGCTGCACCTCCAGGGAAGGAGC
AATGCCTGGAGGCCCCAGGTCAACAACCCAAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATG
AAGGTCACTGGGGTGACCACCCAGGGGGTCAAGAGCCTGCTCACCAGCATGTATGTGAAGGAGTTC
CTGATCAGCTCCAGCCAGGATGGCCACCAGTGGACCCTCTTCTTCCAGAATGGCAAGGTCAAGGTG
TTCCAGGGCAACCAGGACAGCTTCACCCCTGTGGTGAACAGCCTGGACCCCCCCCTCCTGACCAGA
TACCTGAGGATTCACCCCCAGAGCTGGGTCCACCAGATTGCCCTGAGGATGGAGGTCCTGGGATGT
GAGGCCCAGGACCTGTACTGA (SEQ ID NO:98)

Figure 38B

CS23m13-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGTCTGACCTGGGCGAGCTGCCT
GTGGACGCCAGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCTCAGTGGTGTACAAG
AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCAGGCCCCCCTGGATG
GGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATG
GCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCTCTGAGGGCGCCGAG
TATGACGACCAGACCAGCCAGAGGGAGAAGGAGGACGACAAGGTGTTCCCCGGCGGCAGCCACACC
TACGTGTGGCAGGTGCTGAAGGAGAACGGCCCCATGGCCAGCGACCCCCTGTGCCTGACCTACAGC
TACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACTCTGGCCTGATCGGCGCCCTGCTGGTGTGC
AGGGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACCCTGCACAAGTTCATCCTGCTGTTCGCCGTG
TTCGATGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGCCTGATGCAGGACAGGGATGCCGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGGAGCCTGCCCGGCCTG
ATCGGCTGCCACAGGAAGTCTGTGTACTGGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCAC
AGCATCTTCCTGGAGGGCCACACCTTCCTGGTGAGGAACCACAGGCAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTCCTGCCAC
ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCC
CAGCTGAGGATGAAGAACAACGAGGAGGCCGAGGACTATGATGATGACCTGACCGACTCTGAGATG
GACGTGGTGAGGTTTGATGATGACAACAGCCCCAGCTTCATCCAGATCAGGTCTGTGGCCAAGAAG
CACCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCCCCCTGGTG
CTGGCCCCCGACGACAGGAGCTACAAGAGCCAGTACCTGAACAACGGCCCCCAGAGGATCGGCAGG
AAGTACAAGAAGGTCAGATTCATGGCCTACACCGACGAGACCTTCAAGACCAGGGAGGCCATCCAG
CACGAGTCTGGCATCCTGGGCCCCCTGCTGTACGGCGAGGTGGGCGACACCCTGCTGATCATCTTC
AAGAACCAGGCCAGCAGGCCCTACAACATCTACCCCCACGGCATCACCGATGTGAGGCCCCTGTAC
AGCAGGAGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC
AAGTACAAGTGGACCGTGACCGTGGAGGATGGCCCCACCAAGTCTGACCCCAGGTGCCTGACCAGG
TACTACAGCAGCTTCGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATCGGCCCCCTGCTGATC
TGCTACAAGGAGAGCGTGGACCAGAGGGGCAACCAGATCATGTCTGACAAGAGGAACGTGATCCTG
TTCTCTGTGTTCGATGAGAACAGGAGCTGGTATCTGACCGAGAACATCCAGAGGTTCCTGCCCAAC
CCCGCCGGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGC
TACGTGTTCGACAGCCTGCAGCTGTCTGTGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGC
ATCGGCGCCCAGACCGACTTCCTGTCTGTGTTCTTCTCTGGCTACACCTTCAAGCACAAGATGGTG
TACGAGGACACCCTGACCCTGTTCCCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCC
GGCCTGTGGATCCTGGGCTGCCACAACAGCGACTTCAGGAACAGGGGCATGACCGCCCTGCTGAAA
GTCAGCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGACATCAGCGCCTAC
CTGCTGAGCAAGAACAACACCACCTACGTGAACCGCTCCCTGAGCCAGAACCCCCCCGTGCTGAAG
AGGCACCAGAGGGAGATCACCAGGACCACCCTGCAGAGCGACCAGGAGGAGATCGACTATGATGAC
ACCATCAGCGTGGAGATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCC
AGGAGCTTCCAGAAGAAGACCAGGCACTACTTCATCGCCGCCGTGGAGAGGCTGTGGGACTATGGC
ATGAGCAGCAGCCCCCACGTGCTGAGGAACAGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAG

(Continued)

Figure 39A

GTGGTGTTCCAGGAGTTCACCGACGGCAGCTTCACCCAGCCCCTGTACAGAGGCGAGCTGAACGAG
CACCTGGGCCTGCTGGGCCCCTACATCAGGGCCGAGGTGGAGGACAACATCATGGTGACCTTCAGG
AACCAGGCCAGCAGGCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGAGGCAG
GGCGCCGAGCCCAGGAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAG
CACCACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGAC
CTGGAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCTGAAC
CCCGCCCACGGCAGGCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACC
AAGAGCTGGTACTTCACCGAGAACATGGAGAGGAACTGCAGGGCCCCCTGCAACATCCAGATGGAG
GACCCCACCTTCAAGGAGAACTACAGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCC
GGCCTGGTGATGGCCCAGGACCAGAGGATCAGGTGGTATCTGCTGAGCATGGGCAGCAACGAGAAC
ATCCACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGAGGAAGAAGGAGGAGTACAAGATGGCC
CTGTACAACCTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGG
AGGGTGGAGTGCCTGATCGGCGAGCACCTGCACGCCGGCATGAGCACCCTGTTCCTGGTGTACAGC
AACAAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCAGGGACTTCCAGATCACCGCCTCT
GGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGGCTGCACTACAGCGGCAGCATCAACGCCTGG
AGCACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATCCACGGCATC
AAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGC
CTGGACGGCAAGAAGTGGCAGACCTACAGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGC
AACGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCAGGTACATCAGG
CTGCACCCCACCCACTACAGCATCAGGAGCACCCTGCGGATGGAACTGATGGGCTGCGACCTGAAC
AGCTGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATCTCTGACGCCCAGATCACCGCCAGCAGC
TACTTCACCAACATGTTCGCCACCTGGAGCCCCAGCAAGGCCAGGCTGCACCTGCAGGGCAGGAGC
AACGCCTGGAGGCCCCAGGTGAACAACCCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATG
AAGGTGACCGGCGTGACCACCCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTC
CTGATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTGTTCTTCCAGAACGGCAAAGTGAAGGTG
TTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTGGACCCCCCCCCTGCTGACCAGG
TATCTGAGGATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGAGAATGGAAGTGCTGGGATGC
GAGGCCCAGGACCTGTACTGA (SEQ ID NO:99)

Figure 39B

CS23m3-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGTCTGACCTGGGCGAGCTGCCT
GTGGACGCCAGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCTCAGTGGTGTACAAG
AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCAGGCCCCCCTGGATG
GGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATG
GCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCTCTGAGGGCGCCGAG
TATGACGACCAGACCAGCCAGAGGGAGAAGGAGGACGACAAGGTGTTCCCCGGCGGCAGCCACACC
TACGTGTGGCAGGTGCTGAAGGAGAACGGCCCCATGGCCAGCGACCCCCTGTGCCTGACCTACAGC
TACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACTCTGGCCTGATCGGCGCCCTGCTGGTGTGC
AGGGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACCCTGCACAAGTTCATCCTGCTGTTCGCCGTG
TTCGATGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGCCTGATGCAGGACAGGGATGCCGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGGAGCCTGCCCGGCCTG
ATCGGCTGCCACAGGAAGTCTGTGTACTGGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCAC
AGCATCTTCCTGGAGGGCCACACCTTCCTGGTGAGGAACCACAGGCAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCAC
ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCC
CAGCTGAGGATGAAGAACAACGAGGAGGCCGAGGACTATGATGATGACCTGACCGACTCTGAGATG
GACGTGGTGAGGTTTGATGATGACAACAGCCCCAGCTTCATCCAGATCAGGTCTGTGGCCAAGAAG
CACCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCCCCCTGGTG
CTGGCCCCCGACGACAGGAGCTACAAGAGCCAGTACCTGAACAACGGCCCCCAGAGGATCGGCAGG
AAGTACAAGAAGGTCAGATTCATGGCCTACACCGACGAGACCTTCAAGACCAGGGAGGCCATCCAG
CACGAGTCTGGCATCCTGGGCCCCCTGCTGTACGGCGAGGTGGGCGACACCCTGCTGATCATCTTC
AAGAACCAGGCCAGCAGGCCCTACAACATCTACCCCCACGGCATCACCGATGTGAGGCCCCTGTAC
AGCAGGAGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC
AAGTACAAGTGGACCGTGACCGTGGAGGATGGCCCCACCAAGTCTGACCCCAGGTGCCTGACCAGG
TACTACAGCAGCTTCGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATCGGCCCCCTGCTGATC
TGCTACAAGGAGAGCGTGGACCAGAGGGGCAACCAGATCATGTCTGACAAGAGGAACGTGATCCTG
TTCTCTGTGTTCGATGAGAACAGGAGCTGGTATCTGACCGAGAACATCCAGAGGTTCCTGCCCAAC
CCCGCCGGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGC
TACGTGTTCGACAGCCTGCAGCTGTCTGTGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGC
ATCGGCGCCCAGACCGACTTCCTGTCTGTGTTCTTCTCTGGCTACACCTTCAAGCACAAGATGGTG
TACGAGGACACCCTGACCCTGTTCCCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCC
GGCCTGTGGATCCTGGGCTGCCACAACAGCGACTTCAGGAACAGGGGCATGACCGCCCTGCTGAAA
GTCAGCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGACATCAGCGCCTAC
CTGCTGAGCAAGAACAACACCACCTACGTGAACCGCTCCCTGAGCCAGAACCCCCCCGTGCTGAAG
AGGCACCAGAGGGAGATCACCAGGACCACCCTGCAGAGCGACCAGGAGGAGATCGACTATGATGAC
ACCATCAGCGTGGAGATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCC
AGGAGCTTCCAGAAGAAGACCAGGCACTACTTCATCGCCGCCGTGGAGAGGCTGTGGGACTATGGC
ATGAGCAGCAGCCCCCACGTGCTGAGGAACAGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAG

(Continued)

Figure 40A

GTGGTGTTCCAGGAGTTCACCGACGGCAGCTTCACCCAGCCCCTGTACAGAGGCGAGCTGAACGAG
CACCTGGGCCTGCTGGGCCCCTACATCAGGGCCGAGGTGGAGGACAACATCATGGTGACCTTCAGG
AACCAGGCCAGCAGGCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGAGGCAG
GGCGCCGAGCCCAGGAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAG
CACCACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGAC
CTGGAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCTGAAC
CCCGCCCACGGCAGGCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACC
AAGAGCTGGTACTTCACCGAGAACATGGAGAGGAACTGCAGGGCCCCCTGCAACATCCAGATGGAG
GACCCCACCTTCAAGGAGAACTACAGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCC
GGCCTGGTGATGGCCCAGGACCAGAGGATCAGGTGGTATCTGCTGAGCATGGGCAGCAACGAGAAC
ATCCACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGAGGAAGAAGGAGGAGTACAAGATGGCC
CTGTACAACCTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGG
AGGGTGGAGTGCCTGATCGGCGAGCACCTGCACGCCGGCATGAGCACCCTGTTCCTGGTGTACAGC
AACAAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCAGGGACTTCCAGATCACCGCCTCT
GGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGGCTGCACTACAGCGGCAGCATCAACGCCTGG
AGCACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATCCACGGCATC
AAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGC
CTGGACGGCAAGAAGTGGCAGACCTACAGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGC
AACGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCAGGTACATCAGG
CTGCACCCCACCCACTACAGCATCAGGAGCACCCTGCGGATGGAACTGATGGGCTGCGACCTGAAC
AGCTGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATCTCTGACGCCCAGATCACCGCCAGCAGC
TACTTCACCAACATGTTCGCCACCTGGAGCCCCAGCAAGGCCAGGCTGCACCTGCAGGGCAGGAGC
AACGCCTGGAGGCCCCAGGTGAACAACCCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATG
AAGGTGACCGGCGTGACCACCCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTC
CTGATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTGTTCTTCCAGAACGGCAAAGTGAAGGTG
TTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTGGACCCCCCCCTGCTGACCAGG
TATCTGAGGATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGAGAATGGAAGTGCTGGGATGC
GAGGCCCAGGACCTGTACTGA (SEQ ID NO:100)

Figure 40B

CS23m2-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGTCTGACCTGGGCGAGCTGCCT
GTGGACGCCAGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCTCAGTGGTGTACAAG
AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCAGGCCCCCCTGGATG
GGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGGTCACCCTGAAGAACATG
GCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGTCCTCTGAGGGCGCCGAG
TATGACGACCAGACCAGCCAGAGGGAGAAGGAGGACGACAAGGTGTTCCCCGGCAAGAGCCACACC
TACGTGTGGCAGGTGCTGAAGGAGAACGGCCCCACTGCCAGCGACCCCCCCTGCCTGACCTACAGC
TACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACTCTGGCCTGATCGGCGCCCTGCTGGTGTGC
AGGGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACCCTGCACAAGTTCATCCTGCTGTTCGCCGTG
TTCGATGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGCCTGATGCAGGACAGGGATGCCGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGGAGCCTGCCCGGCCTG
ATCGGCTGCCACAGGAAGTCTGTGTACTGGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCAC
AGCATCTTCCTGGAGGGCCACACCTTCCTGGTGAGGAACCACAGGCAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCAC
ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCC
CAGCTGAGGATGAAGAACAACGAGGAGGCCGAGGACTATGATGATGACCTGACCGACTCTGAGATG
GACGTGGTGAGGTTTGATGATGACAACAGCCCCAGCTTCATCCAGATCAGGTCTGTGGCCAAGAAG
CACCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCCCCCTGGTG
CTGGCCCCCGACGACAGGAGCTACAAGAGCCAGTACCTGAACAACGGCCCCCAGAGGATCGGCAGG
AAGTACAAGAAGGTCAGATTCATGGCCTACACCGACGAGACCTTCAAGACCAGGGAGGCCATCCAG
CACGAGTCTGGCATCCTGGGCCCCCTGCTGTACGGCGAGGTGGGCGACACCCTGCTGATCATCTTC
AAGAACCAGGCCAGCAGGCCCTACAACATCTACCCCCACGGCATCACCGATGTGAGGCCCCTGTAC
AGCAGGAGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC
AAGTACAAGTGGACCGTGACCGTGGAGGATGGCCCCACCAAGTCTGACCCCAGGTGCCTGACCAGG
TACTACAGCAGCTTCGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATCGGCCCCCTGCTGATC
TGCTACAAGGAGAGCGTGGACCAGAGGGGCAACCAGATCATGTCTGACAAGAGGAACGTGATCCTG
TTCTCTGTGTTCGATGAGAACAGGAGCTGGTATCTGACCGAGAACATCCAGAGGTTCCTGCCCAAC
CCCGCCGGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGC
TACGTGTTCGACAGCCTGCAGCTGTCTGTGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGC
ATCGGCGCCCAGACCGACTTCCTGTCTGTGTTCTTCTCTGGCTACACCTTCAAGCACAAGATGGTG
TACGAGGACACCCTGACCCTGTTCCCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCC
GGCCTGTGGATCCTGGGCTGCCACAACAGCGACTTCAGGAACAGGGGCATGACCGCCCTGCTGAAA
GTCAGCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGACATCAGCGCCTAC
CTGCTGAGCAAGAACAACGCCATCGAGCCCAGGAGCTTCAGCCAGAACCCCCCCGTGCTGAAGAGG
CACCAGAGGGAGATCACCAGGACCACCCTGCAGAGCGACCAGGAGGAGATCGACTATGATGACACC
ATCAGCGTGGAGATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCCAGG
AGCTTCCAGAAGAAGACCAGGCACTACTTCATCGCCGCCGTGGAGAGGCTGTGGGACTATGGCATG
AGCAGCAGCCCCCACGTGCTGAGGAACAGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAGGTG

(Continued)

Figure 41A

GTGTTCCAGGAGTTCACCGACGGCAGCTTCACCCAGCCCCTGTACAGAGGCGAGCTGAACGAGCAC
CTGGGCCTGCTGGGCCCCTACATCAGGGCCGAGGTGGAGGACAACATCATGGTGACCTTCAGGAAC
CAGGCCAGCAGGCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGAGGCAGGGC
GCCGAGCCCAGGAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAGCAC
CACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTG
GAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCTGAACCCC
GCCCACGGCAGGCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAG
AGCTGGTACTTCACCGAGAACATGGAGAGGAACTGCAGGGCCCCCTGCAACATCCAGATGGAGGAC
CCCACCTTCAAGGAGAACTACAGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCCGGC
CTGGTGATGGCCCAGGACCAGAGGATCAGGTGGTATCTGCTGAGCATGGGCAGCAACGAGAACATC
CACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGAGGAAGAAGGAGGAGTACAAGATGGCCCTG
TACAACCTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGAGG
GTGGAGTGCCTGATCGGCGAGCACCTGCACGCCGGCATGAGCACCCTGTTCCTGGTGTACAGCAAC
AAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCAGGGACTTCCAGATCACCGCCTCTGGC
CAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGGCTGCACTACAGCGGCAGCATCAACGCCTGGAGC
ACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATCCACGGCATCAAG
ACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTG
GACGGCAAGAAGTGGCAGACCTACAGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAAC
GTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCAGGTACATCAGGCTG
CACCCCACCCACTACAGCATCAGGAGCACCCTGCGGATGGAACTGATGGGCTGCGACCTGAACAGC
TGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATCTCTGACGCCCAGATCACCGCCAGCAGCTAC
TTCACCAACATGTTCGCCACCTGGAGCCCCAGCAAGGCCAGGCTGCACCTGCAGGGCAGGAGCAAC
GCCTGGAGGCCCCAGGTGAACAACCCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAG
GTGACCGGCGTGACCACCCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTG
ATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTGTTCTTCCAGAACGGCAAAGTGAAGGTGTTC
CAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTGGACCCCCCCCCTGCTGACCAGGTAT
CTGAGGATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGAGAATGGAAGTGCTGGGATGCGAG
GCCCAGGACCTGTACTGA (SEQ ID NO:101)

Figure 41B

CS23m1-FL-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGTCTGACCTGGGCGAGCTGCCT
GTGGACGCCAGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCTCAGTGGTGTACAAG
AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCAGGCCCCCCTGGATG
GGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATG
GCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCTCTGAGGGCGCCGAG
TATGACGACCAGACCAGCCAGAGGGAGAAGGAGGACGACAAGGTGTTCCCCGGCGGCAGCCACACC
TACGTGTGGCAGGTGCTGAAGGAGAACGGCCCCATGGCCAGCGACCCCCTGTGCCTGACCTACAGC
TACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACTCTGGCCTGATCGGCGCCCTGCTGGTGTGC
AGGGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACCCTGCACAAGTTCATCCTGCTGTTCGCCGTG
TTCGATGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGCCTGATGCAGGACAGGGATGCCGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGGAGCCTGCCCGGCCTG
ATCGGCTGCCACAGGAAGTCTGTGTACTGGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCAC
AGCATCTTCCTGGAGGGCCACACCTTCCTGGTGAGGAACCACAGGCAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTCCTGCCAC
ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCC
CAGCTGAGGATGAAGAACAACGAGGAGGCCGAGGACTATGATGATGACCTGACCGACTCTGAGATG
GACGTGGTGAGGTTTGATGATGACAACAGCCCCAGCTTCATCCAGATCAGGTCTGTGGCCAAGAAG
CACCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCCCCCTGGTG
CTGGCCCCCGACGACAGGAGCTACAAGAGCCAGTACCTGAACAACGGCCCCCAGAGGATCGGCAGG
AAGTACAAGAAGGTCAGATTCATGGCCTACACCGACGAGACCTTCAAGACCAGGGAGGCCATCCAG
CACGAGTCTGGCATCCTGGGCCCCCTGCTGTACGGCGAGGTGGGCGACACCCTGCTGATCATCTTC
AAGAACCAGGCCAGCAGGCCCTACAACATCTACCCCCACGGCATCACCGATGTGAGGCCCCTGTAC
AGCAGGAGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC
AAGTACAAGTGGACCGTGACCGTGGAGGATGGCCCCACCAAGTCTGACCCCAGGTGCCTGACCAGG
TACTACAGCAGCTTCGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATCGGCCCCCTGCTGATC
TGCTACAAGGAGAGCGTGGACCAGAGGGGCAACCAGATCATGTCTGACAAGAGGAACGTGATCCTG
TTCTCTGTGTTCGATGAGAACAGGAGCTGGTATCTGACCGAGAACATCCAGAGGTTCCTGCCCAAC
CCCGCCGGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGC
TACGTGTTCGACAGCCTGCAGCTGTCTGTGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGC
ATCGGCGCCCAGACCGACTTCCTGTCTGTGTTCTTCTCTGGCTACACCTTCAAGCACAAGATGGTG
TACGAGGACACCCTGACCCTGTTCCCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCC
GGCCTGTGGATCCTGGGCTGCCACAACAGCGACTTCAGGAACAGGGGCATGACCGCCCTGCTGAAA
GTCAGCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGACATCAGCGCCTAC
CTGCTGAGCAAGAACAACGCCATCGAGCCCAGGAGCTTCAGCCAGAACCCCCCCGTGCTGAAGAGG
CACCAGAGGGAGATCACCAGGACCACCCTGCAGAGCGACCAGGAGGAGATCGACTATGATGACACC
ATCAGCGTGGAGATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCCAGG
AGCTTCCAGAAGAAGACCAGGCACTACTTCATCGCCGCCGTGGAGAGGCTGTGGGACTATGGCATG
AGCAGCAGCCCCCACGTGCTGAGGAACAGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAGGTG

(Continued)

Figure 42A

GTGTTCCAGGAGTTCACCGACGGCAGCTTCACCCAGCCCCTGTACAGAGGCGAGCTGAACGAGCAC
CTGGGCCTGCTGGGCCCCTACATCAGGGCCGAGGTGGAGGACAACATCATGGTGACCTTCAGGAAC
CAGGCCAGCAGGCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGAGGCAGGGC
GCCGAGCCCAGGAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAGCAC
CACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTG
GAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCTGAACCCC
GCCCACGGCAGGCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAG
AGCTGGTACTTCACCGAGAACATGGAGAGGAACTGCAGGGCCCCCTGCAACATCCAGATGGAGGAC
CCCACCTTCAAGGAGAACTACAGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCCGGC
CTGGTGATGGCCCAGGACCAGAGGATCAGGTGGTATCTGCTGAGCATGGGCAGCAACGAGAACATC
CACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGAGGAAGAAGGAGGAGTACAAGATGGCCCTG
TACAACCTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGAGG
GTGGAGTGCCTGATCGGCGAGCACCTGCACGCCGGCATGAGCACCCTGTTCCTGGTGTACAGCAAC
AAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCAGGGACTTCCAGATCACCGCCTCTGGC
CAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGGCTGCACTACAGCGGCAGCATCAACGCCTGGAGC
ACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATCCACGGCATCAAG
ACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTG
GACGGCAAGAAGTGGCAGACCTACAGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAAC
GTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCCCATCATCGCCAGGTACATCAGGCTG
CACCCCACCCACTACAGCATCAGGAGCACCCTGCGGATGGAACTGATGGGCTGCGACCTGAACAGC
TGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATCTCTGACGCCCAGATCACCGCCAGCAGCTAC
TTCACCAACATGTTCGCCACCTGGAGCCCCAGCAAGGCCAGGCTGCACCTGCAGGGCAGGAGCAAC
GCCTGGAGGCCCCAGGTGAACAACCCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAG
GTGACCGGCGTGACCACCCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTG
ATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTGTTCTTCCAGAACGGCAAAGTGAAGGTGTTC
CAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTGGACCCCCCCCCTGCTGACCAGGTAT
CTGAGGATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGAGAATGGAAGTGCTGGGATGCGAG
GCCCAGGACCTGTACTGA (SEQ ID NO:102)

Figure 42B

CS23m23-FL-NA

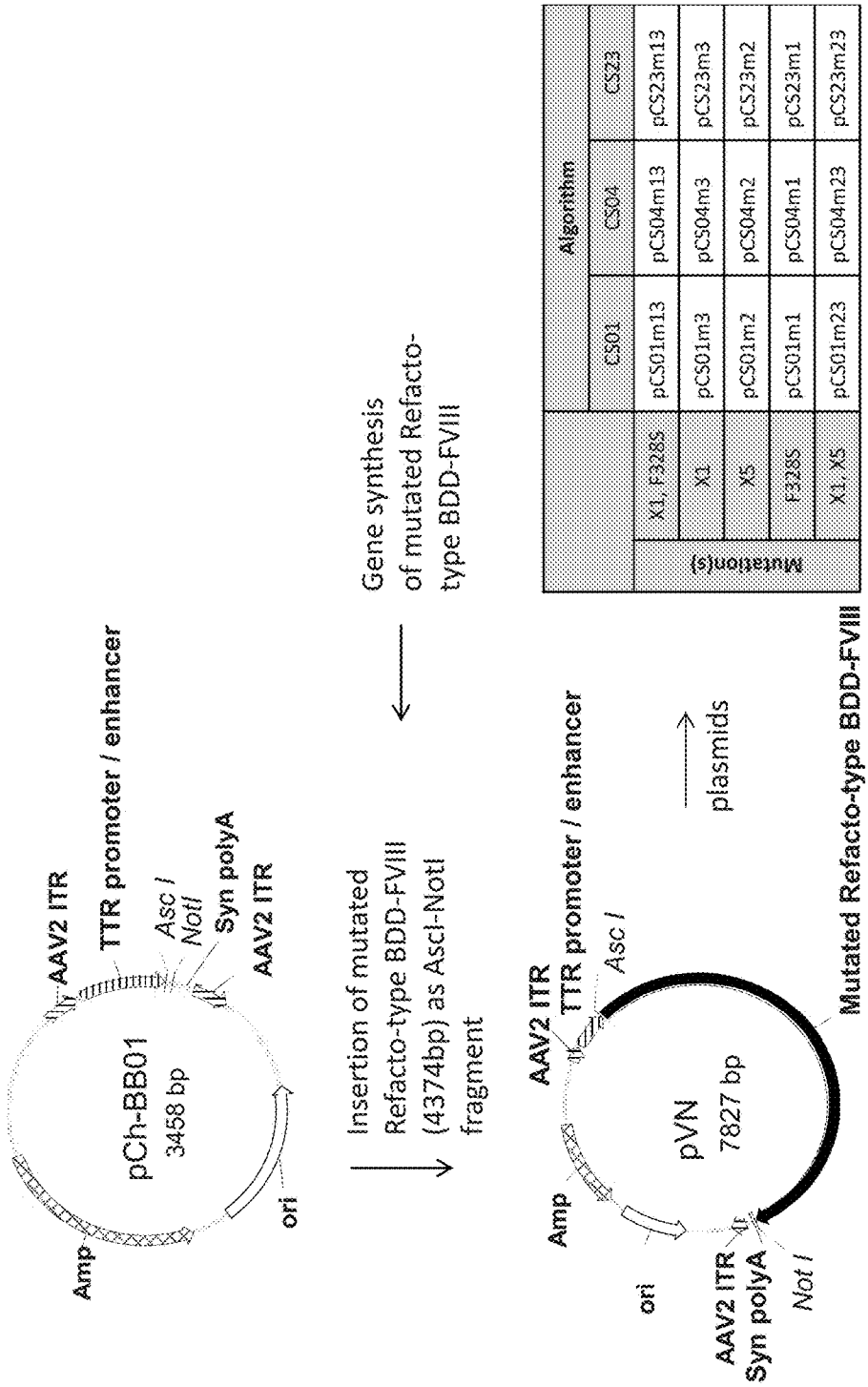
ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGTCTGACCTGGGCGAGCTGCCT
GTGGACGCCAGGTTCCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCTCAGTGGTGTACAAG
AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCAGGCCCCCCTGGATG
GGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGGTCACCCTGAAGAACATG
GCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGTCCTCTGAGGGCGCCGAG
TATGACGACCAGACCAGCCAGAGGGAGAAGGAGGACGACAAGGTGTTCCCCGGCAAGAGCCACACC
TACGTGTGGCAGGTGCTGAAGGAGAACGGCCCCACTGCCAGCGACCCCCCCTGCCTGACCTACAGC
TACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACTCTGGCCTGATCGGCGCCCTGCTGGTGTGC
AGGGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACCCTGCACAAGTTCATCCTGCTGTTCGCCGTG
TTCGATGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGCCTGATGCAGGACAGGGATGCCGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGGAGCCTGCCCGGCCTG
ATCGGCTGCCACAGGAAGTCTGTGTACTGGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCAC
AGCATCTTCCTGGAGGGCCACACCTTCCTGGTGAGGAACCACAGGCAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCAC
ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCC
CAGCTGAGGATGAAGAACAACGAGGAGGCCGAGGACTATGATGATGACCTGACCGACTCTGAGATG
GACGTGGTGAGGTTTGATGATGACAACAGCCCCAGCTTCATCCAGATCAGGTCTGTGGCCAAGAAG
CACCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCCCCCTGGTG
CTGGCCCCCGACGACAGGAGCTACAAGAGCCAGTACCTGAACAACGGCCCCCAGAGGATCGGCAGG
AAGTACAAGAAGGTCAGATTCATGGCCTACACCGACGAGACCTTCAAGACCAGGGAGGCCATCCAG
CACGAGTCTGGCATCCTGGGCCCCCTGCTGTACGGCGAGGTGGGCGACACCCTGCTGATCATCTTC
AAGAACCAGGCCAGCAGGCCCTACAACATCTACCCCCACGGCATCACCGATGTGAGGCCCCTGTAC
AGCAGGAGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC
AAGTACAAGTGGACCGTGACCGTGGAGGATGGCCCCACCAAGTCTGACCCCAGGTGCCTGACCAGG
TACTACAGCAGCTTCGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATCGGCCCCCTGCTGATC
TGCTACAAGGAGAGCGTGGACCAGAGGGGCAACCAGATCATGTCTGACAAGAGGAACGTGATCCTG
TTCTCTGTGTTCGATGAGAACAGGAGCTGGTATCTGACCGAGAACATCCAGAGGTTCCTGCCCAAC
CCCGCCGGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGC
TACGTGTTCGACAGCCTGCAGCTGTCTGTGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGC
ATCGGCGCCCAGACCGACTTCCTGTCTGTGTTCTTCTCTGGCTACACCTTCAAGCACAAGATGGTG
TACGAGGACACCCTGACCCTGTTCCCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCC
GGCCTGTGGATCCTGGGCTGCCACAACAGCGACTTCAGGAACAGGGGCATGACCGCCCTGCTGAAA
GTCAGCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGACATCAGCGCCTAC
CTGCTGAGCAAGAACAACACCACCTACGTGAACCGCTCCCTGAGCCAGAACCCCCCCGTGCTGAAG
AGGCACCAGAGGGAGATCACCAGGACCACCCTGCAGAGCGACCAGGAGGAGATCGACTATGATGAC
ACCATCAGCGTGGAGATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCC
AGGAGCTTCCAGAAGAAGACCAGGCACTACTTCATCGCCGCCGTGGAGAGGCTGTGGGACTATGGC
ATGAGCAGCAGCCCCCACGTGCTGAGGAACAGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAG

(Continued)

Figure 43A

GTGGTGTTCCAGGAGTTCACCGACGGCAGCTTCACCCAGCCCCTGTACAGAGGCGAGCTGAACGAG
CACCTGGGCCTGCTGGGCCCCTACATCAGGGCCGAGGTGGAGGACAACATCATGGTGACCTTCAGG
AACCAGGCCAGCAGGCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGAGGCAG
GGCGCCGAGCCCAGGAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAG
CACCACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGAC
CTGGAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCTGAAC
CCCGCCCACGGCAGGCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACC
AAGAGCTGGTACTTCACCGAGAACATGGAGAGGAACTGCAGGGCCCCCTGCAACATCCAGATGGAG
GACCCCACCTTCAAGGAGAACTACAGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCC
GGCCTGGTGATGGCCCAGGACCAGAGGATCAGGTGGTATCTGCTGAGCATGGGCAGCAACGAGAAC
ATCCACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGAGGAAGAAGGAGGAGTACAAGATGGCC
CTGTACAACCTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGG
AGGGTGGAGTGCCTGATCGGCGAGCACCTGCACGCCGGCATGAGCACCCTGTTCCTGGTGTACAGC
AACAAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCAGGGACTTCCAGATCACCGCCTCT
GGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGGCTGCACTACAGCGGCAGCATCAACGCCTGG
AGCACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATCCACGGCATC
AAGACCCAGGGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGC
CTGGACGGCAAGAAGTGGCAGACCTACAGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGC
AACGTGGACAGCAGCGGCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCAGGTACATCAGG
CTGCACCCCACCCACTACAGCATCAGGAGCACCCTGCGGATGGAACTGATGGGCTGCGACCTGAAC
AGCTGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATCTCTGACGCCCAGATCACCGCCAGCAGC
TACTTCACCAACATGTTCGCCACCTGGAGCCCCAGCAAGGCCAGGCTGCACCTGCAGGGCAGGAGC
AACGCCTGGAGGCCCCAGGTGAACAACCCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATG
AAGGTGACCGGCGTGACCACCCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTC
CTGATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTGTTCTTCCAGAACGGCAAAGTGAAGGTG
TTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTGGACCCCCCCCCTGCTGACCAGG
TATCTGAGGATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGAGAATGGAAGTGCTGGGATGC
GAGGCCCAGGACCTGTACTGA (SEQ ID NO:103)

Figure 43B



		Algorithm		
		CS01	CS04	CS23
Mutation(s)	X1, F328S	pCS01m13	pCS04m13	pCS23m13
	X1	pCS01m3	pCS04m3	pCS23m3
	X5	pCS01m2	pCS04m2	pCS23m2
	F328S	pCS01m1	pCS04m1	pCS23m1
	X1, X5	pCS01m23	pCS04m23	pCS23m23

Figure 44

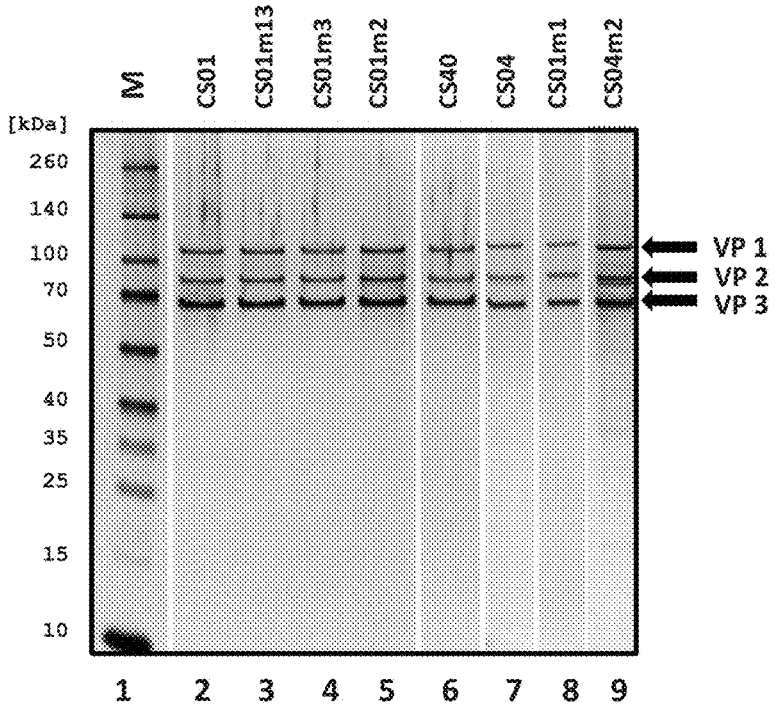


Figure 45

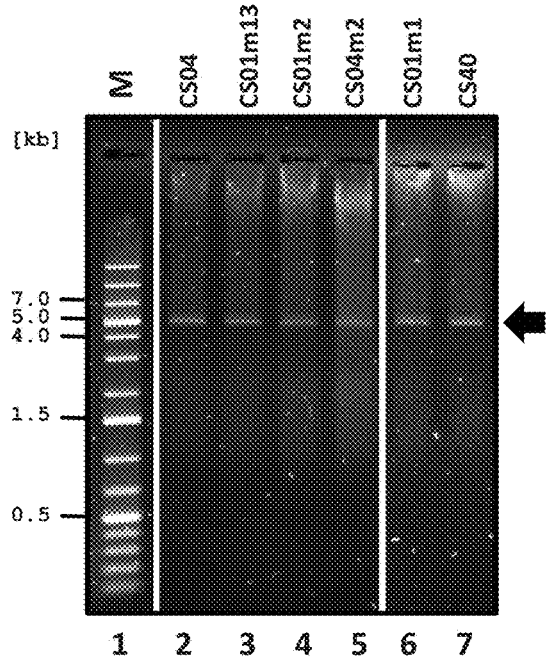


Figure 46

CS01-HC-NA

gcc
accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg
ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac
acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt
gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat
gacactgtgg tcatcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg
ggagtctcat actggaaagc ctctgaaggg gctgagtatg atgaccagac atcccagaga
gagaaagagg atgacaaggt gttccctggg ggatctcaca cctatgtgtg gcaagtcctc
aaggagaatg gacccatggc atctgaccca ctctgcctga catactccta cctttctcat
gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa
ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc
tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat
gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca
ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg
acaaccccctg aagtgcactc catttcctg gagggacaca ccttcctggt caggaaccac
agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg
gaccttggac agttcctgct gttctgccac atctcttccc accagcatga tggcatggaa
gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag
gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat
gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca
tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc
cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga
aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc
attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg
ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact
gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc
cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca
acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga
gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag
agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag
aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg
caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg
tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct
attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag
atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc
atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga
atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac
tcttatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccaga
(SEQ ID NO:24X)

Figure 47

CS01-LC-NA

g agatcaccag gacaaccctc
cagtctgacc aggaagagat tgactatgat gacaccattt ctgtggagat gaagaaggag
gactttgaca tctatgatga ggacgagaac cagtctccaa gatcattcca gaagaagaca
agacactact tcattgctgc tgtggaaaga ctgtgggact atggcatgtc ttcctctccc
catgtcctca ggaacagggc acagtctggc tctgtgccac agttcaagaa agtggtcttc
caggagttca ctgatggctc attcacccag cccctgtaca gaggggaact gaatgagcac
ctgggactcc tgggaccata catcagggct gaggtggaag acaacatcat ggtgacattc
agaaaccagg cctccaggcc ctacagcttc tactcttccc tcatcagcta tgaggaagac
cagagacaag gggctgagcc aagaaagaac tttgtgaaac ccaatgaaac caagacctac
ttctggaaag tccagcacca catggcaccc accaaggatg agtttgactg caaggcctgg
gcatacttct ctgatgtgga cctggagaaa gatgtgcact ctggcctgat tggcccactc
ctggtctgcc acaccaacac cctgaaccct gcacatggaa ggcaagtgac tgtgcaggag
tttgccctct tcttcaccat ctttgatgaa accaagtcat ggtacttcac tgagaacatg
gagagaaact gcagagcacc atgcaacatt cagatggaag accccacctt caaggagaac
tacaggttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggca
caggaccaga gaatcagatg gtacctgctt tctatgggat ccaatgagaa cattcactcc
atccacttct ctgggcatgt cttcactgtg agaaagaagg aggaatacaa gatggccctg
tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc
tggagggtgg aatgcctcat tggggagcac ctgcatgctg gcatgtcaac cctgttcctg
gtctacagca acaagtgcca gacacccctg ggaatggcct ctggccacat cagggacttc
cagatcactg cctctggcca gtatggccag tgggcaccca aactggccag gctccactac
tctggctcca tcaatgcatg gtcaaccaag gagccattct cttggatcaa ggtggacctg
ctggcaccca tgatcattca tggcatcaag acacaggggg caagacagaa attctcctct
ctgtacatct cacagttcat catcatgtac tctctggatg gcaagaagtg gcagacatac
agaggcaact ccactggcac cctcatggtc ttctttggca atgtggacag ctctggcatc
aagcacaaca tcttcaaccc tcccatcatt gccagataca tcaggctgca ccccacccac
tactcaatca gatcaaccct caggatggaa ctgatgggat gtgacctgaa ctcctgctca
atgcccctgg gaatggagag caaggccatt tctgatgccc agatcactgc atcctcttac
ttcaccaaca tgtttgccac ctggtcacca tcaaaagcca ggctgcacct ccagggaaga
agcaatgcct ggagacccca ggtcaacaac ccaaaggaat ggctgcaagt ggacttccag
aagacaatga aagtcactgg ggtgacaacc caggggqtca agtctctgct cacctcaatg
tatgtgaagg agttcctgat ctcttcctca caggatggcc accagtggac actcttcttc
cagaatggca aagtcaaggt gttccagggc aaccaggact ctttcacacc tgtggtgaac
tcactggacc ccccccctcct gacaagatac ctgagaattc acccccagtc ttgggtccac
cagattgccc tgagaatgga agtcctggga tgtgaggcac aagacctgta c
(SEQ ID NO:25)

Figure 48

CS01Δ(760-1667) - CS01-SC1-NA

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGGAGATAC
TACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCTGTGGATGCCAGG
TTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAGAAGACACTCTTTGTGGAA
TTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATGGGACTCCTGGGACCCACCATTCAG
GCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATGGCATCCCACCCTGTGTCTCTGCATGCTGTG
GGAGTCTCATACTGGAAAGCCTCTGAAGGGGCTGAGTATGATGACCAGACATCCCAGAGAGAGAAAGAGGAT
GACAAGGTGTTCCCTGGGGGATCTCACACCTATGTGTGGCAAGTCCTCAAGGAGAATGGACCCATGGCATCT
GACCCACTCTGCCTGACATACTCCTACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATT
GGGGCACTGCTGGTGTGCAGGGAAGGATCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTC
CTGTTTGCTGTCTTTGATGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGAT
GCTGCCTCTGCCAGGGCATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCACTCCATT
TTCCTGGAGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCTCCCATCACCTTC
CTCACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTTCTGCCACATCTCTTCCCACCAGCAT
GATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCACAGCTCAGGATGAAGAACAATGAG
GAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATGGATGTGGTCAGATTTGATGATGACAACTCT
CCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAACACCCCAAGACATGGGTGCACTACATTGCTGCTGAG
GAAGAGGACTGGGACTATGCACCACTGGTCCTGGCCCCTGATGACAGGAGCTACAAGTCTCAGTACCTCAAC
AATGGCCCACAAAGAATTGGAAGAAAGTACAAGAAAGTCAGATTCATGGCCTACACTGATGAAACCTTCAAG
ACAAGAGAAGCCATTCAGCATGAGTCTGGCATTCTGGGACCACTCCTGTATGGGGAAGTGGGAGACACCCTG
CTCATCATCTTCAAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCC
CTGTACAGCAGGAGACTGCCAAAAGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGATACTAC
TCCTCTTTTGTGAACATGGAGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATCTGCTACAAGGAG
TCTGTGGACCAGAGAGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTGTTCTCTGTCTTTGATGAG
AACAGATCATGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAACCCTGCTGGGGTGCAACTGGAAGAC
CCTGAGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGCTATGTGTTTGACTCTCTCCAGCTTTCTGTC
TGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCTATTGGGGCACAAACTGACTTCCTTTCTGTCTTCTTC
TCTGGATACACCTTCAAGCACAAGATGGTGTATGAGGACACCCTGACACTCTTCCCATTCTCTGGGGAAACT
GTGTTCATGAGCATGGAGAACCCTGGACTGTGGATTCTGGGATGCCACAACTCTGACTTCAGAAACAGGGGA
ATGACTGCACTGCTCAAAGTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACTCTTATGAGGAC
ATCTCTGCCTACCTGCTCAGCAAGAACAATGCCATTGAGCCCAGAGAGATCACCAGGACAACCCTCCAGTCT
GACCAGGAAGAGATTGACTATGATGACACCATTTCTGTGGAGATGAAGAAGGAGGACTTTGACATCTATGAT
GAGGACGAGAACCAGTCTCCAAGATCATTCCAGAAGAAGACAAGACACTACTTCATTGCTGCTGTGGAAAGA
CTGTGGGACTATGGCATGTCTTCCTCTCCCCATGTCCTCAGGAACAGGGCACAGTCTGGCTCTGTGCCACAG
TTCAAGAAAGTGGTCTTCCAGGAGTTCACTGATGGCTCATTCACCCAGCCCCTGTACAGAGGGGAACTGAAT
GAGCACCTGGGACTCCTGGGACCATACATCAGGGCTGAGGTGGAAGACAACATCATGGTGACATTCAGAAAC
CAGGCCTCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAGCTATGAGGAAGACCAGAGACAAGGGGCTGAG
CCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCACCACATGGCACCC

(Continued)

Figure 49A

ACCAAGGATGAGTTTGACTGCAAGGCCTGGGCATACTTCTCTGATGTGGACCTGGAGAAAGATGTGCACTCT
GGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCTGCACATGGAAGGCAAGTGACTGTG
CAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAGTCATGGTACTTCACTGAGAACATGGAGAGA
AACTGCAGAGCACCATGCAACATTCAGATGGAAGACCCCACCTTCAAGGAGAACTACAGGTTCCATGCCATC
AATGGCTACATCATGGACACCCTGCCTGGGCTTGTCATGGCACAGGACCAGAGAATCAGATGGTACCTGCTT
TCTATGGGATCCAATGAGAACATTCACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAG
GAATACAAGATGGCCCTGTACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCT
GGCATCTGGAGGGTGGAATGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTCCTGGTCTAC
AGCAACAAGTGCCAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGC
CAGTATGGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCATCAATGCATGGTCAACCAAG
GAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATTCATGGCATCAAGACACAGGGGGCA
AGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCATGTACTCTCTGGATGGCAAGAAGTGGCAG
ACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTTCTTTGGCAATGTGGACAGCTCTGGCATCAAGCAC
AACATCTTCAACCCTCCCATCATTGCCAGATACATCAGGCTGCACCCCACCCACTACTCAATCAGATCAACC
CTCAGGATGGAACTGATGGGATGTGACCTGAACTCCTGCTCAATGCCCCTGGGAATGGAGAGCAAGGCCATT
TCTGATGCCCAGATCACTGCATCCTCTTACTTCACCAACATGTTTGCCACCTGGTCACCATCAAAAGCCAGG
CTGCACCTCCAGGGAAGAAGCAATGCCTGGAGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGAC
TTCCAGAAGACAATGAAAGTCACTGGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTG
AAGGAGTTCCTGATCTCTTCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAG
GTGTTCCAGGGCAACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGATAC
CTGAGAATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGTGAGGCACAA
GACCTGTACTGA (SEQ ID NO:26)

Figure 49B

CS01Δ(772-1667) - CS01-SC2-NA

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACACTCTTTGTGGAATTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCATCACCCTCAAGAACATG
GCATCCCACCCTGTGTCTCTGCATGCTGTGGGAGTCTCATACTGGAAAGCCTCTGAAGGGGCTGAG
TATGATGACCAGACATCCCAGAGAGAGAAAGAGGATGACAAGGTGTTCCCTGGGGGATCTCACACC
TATGTGTGGCAAGTCCTCAAGGAGAATGGACCCATGGCATCTGACCCACTCTGCCTGACATACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCACTGCTGGTGTGC
AGGGAAGGATCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGATGCTGCC
TCTGCCAGGGCATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCAC
TCCATTTTCCTGGAGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCT
CCCATCACCTTCCTCACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTTCTGCCAC
ATCTCTTCCCACCAGCATGATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCAGATTTGATGATGACAACTCTCCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAA
CACCCCAAGACATGGGTGCACTACATTGCTGCTGAGGAAGAGGACTGGGACTATGCACCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGTCTCAGTACCTCAACAATGGCCCACAAAGAATTGGAAGA
AAGTACAAGAAAGTCAGATTCATGGCCTACACTGATGAAACCTTCAAGACAAGAGAAGCCATTCAG
CATGAGTCTGGCATTCTGGGACCACTCCTGTATGGGGAAGTGGGAGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCAGGAGACTGCCAAAAGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGA
TACTACTCCTCTTTTGTGAACATGGAGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGAGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGATCATGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAAC
CCTGCTGGGGTGCAACTGGAAGACCCTGAGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACTCTCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCACAAACTGACTTCCTTTCTGTCTTCTTCTCTGGATACACCTTCAAGCACAAGATGGTG
TATGAGGACACCCTGACACTCTTCCCATTCTCTGGGGAAACTGTGTTCATGAGCATGGAGAACCCT
GGACTGTGGATTCTGGGATGCCACAACTCTGACTTCAGAAACAGGGGAATGACTGCACTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACTCTTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATGCCATTGAGCCCAGAAGCTTCTCTCAGAATTCCAGACACCCCAGCACC
AGGGAGATCACCAGGACAACCCTCCAGTCTGACCAGGAAGAGATTGACTATGATGACACCATTTCT
GTGGAGATGAAGAAGGAGGACTTTGACATCTATGATGAGGACGAGAACCAGTCTCCAAGATCATTC

(Continued)

Figure 50A

CAGAAGAAGACAAGACACTACTTCATTGCTGCTGTGGAAAGACTGTGGGACTATGGCATGTCTTCC
TCTCCCCATGTCCTCAGGAACAGGGCACAGTCTGGCTCTGTGCCACAGTTCAAGAAAGTGGTCTTC
CAGGAGTTCACTGATGGCTCATTCACCCAGCCCCTGTACAGAGGGGAACTGAATGAGCACCTGGGA
CTCCTGGGACCATACATCAGGGCTGAGGTGGAAGACAACATCATGGTGACATTCAGAAACCAGGCC
TCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAGCTATGAGGAAGACCAGAGACAAGGGGCTGAG
CCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCACCACATG
GCACCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCATACTTCTCTGATGTGGACCTGGAGAAA
GATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCTGCACAT
GGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAGTCATGG
TACTTCACTGAGAACATGGAGAGAAACTGCAGAGCACCATGCAACATTCAGATGGAAGACCCCACC
TTCAAGGAGAACTACAGGTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGGCTTGTC
ATGGCACAGGACCAGAGAATCAGATGGTACCTGCTTTCTATGGGATCCAATGAGAACATTCACTCC
ATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAGGAATACAAGATGGCCCTGTACAAC
CTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGGAGGGTGGAA
TGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTCCTGGTCTACAGCAACAAGTGC
CAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGCCAGTAT
GGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCATCAATGCATGGTCAACCAAG
GAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATTCATGGCATCAAGACACAG
GGGGCAAGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCATGTACTCTCTGGATGGC
AAGAAGTGGCAGACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTTCTTTGGCAATGTGGAC
AGCTCTGGCATCAAGCACAACATCTTCAACCCTCCCATCATTGCCAGATACATCAGGCTGCACCCC
ACCCACTACTCAATCAGATCAACCCTCAGGATGGAACTGATGGGATGTGACCTGAACTCCTGCTCA
ATGCCCCTGGGAATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCATCCTCTTACTTCACC
AACATGTTTGCCACCTGGTCACCATCAAAAGCCAGGCTGCACCTCCAGGGAAGAAGCAATGCCTGG
AGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGACTTCCAGAAGACAATGAAAGTCACT
GGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTGAAGGAGTTCCTGATCTCT
TCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAGGTGTTCCAGGGC
AACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGATACCTGAGA
ATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGTGAGGCACAA
GACCTGTACTGA (SEQ ID NO:27)

Figure 50B

CS23A(760-1667) - CS23-SC1-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGGAGATAC
TACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGTCTGACCTGGGCGAGCTGCCTGTGGACGCCAGG
TTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCTCAGTGGTGTACAAGAAGACCCTGTTCGTGGAG
TTCACCGACCACCTGTTCAACATCGCCAAGCCCAGGCCCCCCTGGATGGGCCTGCTGGGCCCCACCATCCAG
GCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAGCCACCCCGTGAGCCTGCACGCCGTG
GGCGTGAGCTACTGGAAGGCCTCTGAGGGCGCCGAGTATGACGACCAGACCAGCCAGAGGGAGAAGGAGGAC
GACAAGGTGTTCCCCGGCGGCAGCCACACCTACGTGTGGCAGGTGCTGAAGGAGAACGGCCCCATGGCCAGC
GACCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACTCTGGCCTGATC
GGCGCCCTGCTGGTGTGCAGGGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACCCTGCACAAGTTCATCCTG
CTGTTCGCCGTGTTCGATGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGCCTGATGCAGGACAGGGAT
GCCGCCTCTGCCAGGGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGGAGCCTGCCCGGCCTG
ATCGGCTGCCACAGGAAGTCTGTGTACTGGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCACAGCATC
TTCCTGGAGGGCCACACCTTCCTGGTGAGGAACCACAGGCAGGCCAGCCTGGAGATCAGCCCCATCACCTTC
CTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCACATCAGCAGCCACCAGCAC
GACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCCCAGCTGAGGATGAAGAACAACGAG
GAGGCCGAGGACTATGATGATGACCTGACCGACTCTGAGATGGACGTGGTGAGGTTTGATGATGACAACAGC
CCCAGCTTCATCCAGATCAGGTCTGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTACATCGCCGCCGAG
GAGGAGGACTGGGACTACGCCCCCCTGGTGCTGGCCCCCGACGACAGGAGCTACAAGAGCCAGTACCTGAAC
AACGGCCCCCAGAGGATCGGCAGGAAGTACAAGAAGGTCAGATTCATGGCCTACACCGACGAGACCTTCAAG
ACCAGGGAGGCCATCCAGCACGAGTCTGGCATCCTGGGCCCCCTGCTGTACGGCGAGGTGGGCGACACCCTG
CTGATCATCTTCAAGAACCAGGCCAGCAGGCCCTACAACATCTACCCCCACGGCATCACCGATGTGAGGCCC
CTGTACAGCAGGAGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC
AAGTACAAGTGGACCGTGACCGTGGAGGATGGCCCCACCAAGTCTGACCCCAGGTGCCTGACCAGGTACTAC
AGCAGCTTCGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATCGGCCCCCTGCTGATCTGCTACAAGGAG
AGCGTGGACCAGAGGGGCAACCAGATCATGTCTGACAAGAGGAACGTGATCCTGTTCTCTGTGTTCGATGAG
AACAGGAGCTGGTATCTGACCGAGAACATCCAGAGGTTCCTGCCCAACCCCGCCGGCGTGCAGCTGGAGGAC
CCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGCTACGTGTTCGACAGCCTGCAGCTGTCTGTG
TGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACCGACTTCCTGTCTGTGTTCTTC
TCTGGCTACACCTTCAAGCACAAGATGGTGTACGAGGACACCCTGACCCTGTTCCCCTTCAGCGGCGAGACC
GTGTTCATGAGCATGGAGAACCCCGGCCTGTGGATCCTGGGCTGCCACAACAGCGACTTCAGGAACAGGGGC
ATGACCGCCCTGCTGAAAGTCAGCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGAC
ATCAGCGCCTACCTGCTGAGCAAGAACAACGCCATCGAGCCCAGGGAGATCACCAGGACCACCCTGCAGAGC
GACCAGGAGGAGATCGACTATGATGACACCATCAGCGTGGAGATGAAGAAGGAGGACTTCGACATCTACGAC
GAGGACGAGAACCAGAGCCCCAGGAGCTTCCAGAAGAAGACCAGGCACTACTTCATCGCCGCCGTGGAGAGG
CTGTGGGACTATGGCATGAGCAGCAGCCCCCACGTGCTGAGGAACAGGGCCCAGAGCGGCAGCGTGCCCCAG
TTCAAGAAGGTGGTGTTCCAGGAGTTCACCGACGGCAGCTTCACCCAGCCCCTGTACAGAGGCGAGCTGAAC
GAGCACCTGGGCCTGCTGGGCCCCTACATCAGGGCCGAGGTGGAGGACAACATCATGGTGACCTTCAGGAAC
CAGGCCAGCAGGCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGAGGCAGGGCGCCGAG

(Continued)

Figure 51A

CCCAGGAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAGCACCACATGGCCCCC
ACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTGGAGAAGGACGTGCACAGC
GGCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCTGAACCCCGCCCACGGCAGGCAGGTGACCGTG
CAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAGAGCTGGTACTTCACCGAGAACATGGAGAGG
AACTGCAGGGCCCCCTGCAACATCCAGATGGAGGACCCCACCTTCAAGGAGAACTACAGGTTCCACGCCATC
AACGGCTACATCATGGACACCCTGCCCGGCCTGGTGATGGCCCAGGACCAGACGATCAGGTGGTATCTGCTG
AGCATGGGCAGCAACGAGAACATCCACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGAGGAAGAAGGAG
GAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCC
GGCATCTGGAGGGTGGAGTGCCTGATCGGCGAGCACCTGCACGCCGGCATGAGCACCCTGTTCCTGGTGTAC
AGCAACAAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCAGGGACTTCCAGATCACCGCCTCTGGC
CAGTACGGCCAGTGGGCCCCCAAGCTGGCCAGGCTGCACTACAGCGGCAGCATCAACGCCTGGAGCACCAAG
GAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATCCACGGCATCAAGACCCAGGGCGCC
AGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGACGGCAAGAAGTGGCAG
ACCTACAGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAACGTGGACAGCAGCGGCATCAAGCAC
AACATCTTCAACCCCCCCATCATCGCCAGGTACATCAGGCTGCACCCCACCCACTACAGCATCAGGAGCACC
CTGCGGATGGAACTGATGGGCTGCGACCTGAACAGCTGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATC
TCTGACGCCCAGATCACCGCCAGCAGCTACTTCACCAACATGTTCGCCACCTGGAGCCCCAGCAAGGCCAGG
CTGCACCTGCAGGGCAGGAGCAACGCCTGGAGGCCCCAGGTGAACAACCCCAAGGAGTGGCTGCAGGTGGAC
TTCCAGAAGACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTG
AAGGAGTTCCTGATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTGTTCTTCCAGAACGGCAAAGTGAAG
GTGTTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTGGACCCCCCCCTGCTGACCAGGTAT
CTGAGGATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGAGAATGGAAGTGCTGGGATGCGAGGCCCAG
GACCTGTACTGA (SEQ ID NO:28)

Figure 51B

CS23Δ(772-1667) - CS23-SC2-NA

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGTCTGACCTGGGCGAGCTGCCT
GTGGACGCCAGGTTCCCCCCCAGAGTGCCCAAGAGCTTCCCCTTCAACACCTCAGTGGTGTACAAG
AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCAGGCCCCCCTGGATG
GGCCTGCTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATG
GCCAGCCACCCCGTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCTCTGAGGGCGCCGAG
TATGACGACCAGACCAGCCAGAGGGAGAAGGAGGACGACAAGGTGTTCCCCGGCGGCAGCCACACC
TACGTGTGGCAGGTGCTGAAGGAGAACGGCCCCATGGCCAGCGACCCCCTGTGCCTGACCTACAGC
TACCTGAGCCACGTGGACCTGGTGAAGGACCTGAACTCTGGCCTGATCGGCGCCCTGCTGGTGTGC
AGGGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACCCTGCACAAGTTCATCCTGCTGTTCGCCGTG
TTCGATGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGCCTGATGCAGGACAGGGATGCCGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACCGTGAACGGCTACGTGAACAGGAGCCTGCCCGGCCTG
ATCGGCTGCCACAGGAAGTCTGTGTACTGGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCAC
AGCATCTTCCTGGAGGGCCACACCTTCCTGGTGAGGAACCACAGGCAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCAC
ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCC
CAGCTGAGGATGAAGAACAACGAGGAGGCCGAGGACTATGATGATGACCTGACCGACTCTGAGATG
GACGTGGTGAGGTTTGATGATGACAACAGCCCCAGCTTCATCCAGATCAGGTCTGTGGCCAAGAAG
CACCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCCCCCTGGTG
CTGGCCCCCGACGACAGGAGCTACAAGAGCCAGTACCTGAACAACGGCCCCCAGAGGATCGGCAGG
AAGTACAAGAAGGTCAGATTCATGGCCTACACCGACGAGACCTTCAAGACCAGGGAGGCCATCCAG
CACGAGTCTGGCATCCTGGGCCCCCTGCTGTACGGCGAGGTGGGCGACACCCTGCTGATCATCTTC
AAGAACCAGGCCAGCAGGCCCTACAACATCTACCCCCACGGCATCACCGATGTGAGGCCCCTGTAC
AGCAGGAGGCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTTC
AAGTACAAGTGGACCGTGACCGTGGAGGATGGCCCCACCAAGTCTGACCCCAGGTGCCTGACCAGG
TACTACAGCAGCTTCGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATCGGCCCCCTGCTGATC
TGCTACAAGGAGAGCGTGGACCAGAGGGGCAACCAGATCATGTCTGACAAGAGGAACGTGATCCTG
TTCTCTGTGTTCGATGAGAACAGGAGCTGGTATCTGACCGAGAACATCCAGAGGTTCCTGCCCAAC
CCCGCCGGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGC
TACGTGTTCGACAGCCTGCAGCTGTCTGTGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGC
ATCGGCGCCCAGACCGACTTCCTGTCTGTGTTCTTCTCTGGCTACACCTTCAAGCACAAGATGGTG
TACGAGGACACCCTGACCCTGTTCCCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCC
GGCCTGTGGATCCTGGGCTGCCACAACAGCGACTTCAGGAACAGGGGCATGACCGCCCTGCTGAAA
GTCAGCAGCTGCGACAAGAACACCGGCGACTACTACGAGGACAGCTACGAGGACATCAGCGCCTAC
CTGCTGAGCAAGAACAACGCCATCGAGCCCAGGAGCTTCAGCCAGAACTCCAGACACCCCAGCACC

(Continued)

Figure 52A

AGGGAGATCACCAGGACCACCCTGCAGAGCGACCAGGAGGAGATCGACTATGATGACACCATCAGC
GTGGAGATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCCAGGAGCTTC
CAGAAGAAGACCAGGCACTACTTCATCGCCGCCGTGGAGAGGCTGTGGGACTATGGCATGAGCAGC
AGCCCCCACGTGCTGAGGAACAGGGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAGGTGGTGTTC
CAGGAGTTCACCGACGGCAGCTTCACCCAGCCCCTGTACAGAGGCGAGCTGAACGAGCACCTGGGC
CTGCTGGGCCCCTACATCAGGGCCGAGGTGGAGGACAACATCATGGTGACCTTCAGGAACCAGGCC
AGCAGGCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGAGGCAGGGCGCCGAG
CCCAGGAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAGCACCACATG
GCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTGGAGAAG
GACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCTGAACCCCGCCCAC
GGCAGGCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAGAGCTGG
TACTTCACCGAGAACATGGAGAGGAACTGCAGGGCCCCCTGCAACATCCAGATGGAGGACCCCACC
TTCAAGGAGAACTACAGGTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCCGGCCTGGTG
ATGGCCCAGGACCAGAGGATCAGGTGGTATCTGCTGAGCATGGGCAGCAACGAGAACATCCACAGC
ATCCACTTCAGCGGCCACGTGTTCACCGTGAGGAAGAAGGAGGAGTACAAGATGGCCCTGTACAAC
CTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGAGGGTGGAG
TGCCTGATCGGCGAGCACCTGCACGCCGGCATGAGCACCCTGTTCCTGGTGTACAGCAACAAGTGC
CAGACCCCCCTGGGCATGGCCAGCGGCCACATCAGGGACTTCCAGATCACCGCCTCTGGCCAGTAC
GGCCAGTGGGCCCCCAAGCTGGCCAGGCTGCACTACAGCGGCAGCATCAACGCCTGGAGCACCAAG
GAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATCCACGGCATCAAGACCCAG
GGCGCCAGGCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTGGACGGC
AAGAAGTGGCAGACCTACAGGGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAACGTGGAC
AGCAGCGGCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCAGGTACATCAGGCTGCACCCC
ACCCACTACAGCATCAGGAGCACCCTGCGGATGGAACTGATGGGCTGCGACCTGAACAGCTGCAGC
ATGCCCCTGGGCATGGAGAGCAAGGCCATCTCTGACGCCCAGATCACCGCCAGCAGCTACTTCACC
AACATGTTCGCCACCTGGAGCCCCAGCAAGGCCAGGCTGCACCTGCAGGGCAGGAGCAACGCCTGG
AGGCCCCAGGTGAACAACCCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAGGTGACC
GGCGTGACCACCCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTGATCAGC
AGCAGCCAGGACGGCCACCAGTGGACCCTGTTCTTCCAGAACGGCAAAGTGAAGGTGTTCCAGGGC
AACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTGGACCCCCCCCCTGCTGACCAGGTATCTGAGG
ATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGAGAATGGAAGTGCTGGGATGCGAGGCCCAG
GACCTGTACTGA (SEQ ID NO:29)

Figure 52B

CS01m23-FL-AA (SEQ ID NO: 104)

MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFN
TSVVYKKTLFVEFTDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVVTLKNMASHPVSLHAV
GVSYWKSSEGAEYDDQTSQREKEDDKVFPGKSHTYVWQVLKENGPTASDPPCLTYSYLSH
VDLVKDLNSGLIGALLVCREGSLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRD
AASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNH
RQASLEISPITFLTAQTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNE
EAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKKHPKTWVHYIAAEEEDWDYAPLVLA
PDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQHESGILGPLLYGEVGDTL
LIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIFKYKWTVTVEDGP
TKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVILFSVFDE
NRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILS
IGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRG
MTALLKVSSCDKNTGDYYEDSYEDISAYLLSKNNTTYVNRSLSQNPPVLKRHQREITRTT
LQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSS
PHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIMVT
FRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKA
WAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTEN
MERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIH
SIHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLF
LVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVD
LLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSG
IKHNIFNPPIIARYIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASS
YFTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTS
MYVKEFLISSSQDGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWV
HQIALRMEVLGCEAQDLY

Figure 53

CS04m3-FL-AA (SEQ ID NO: 105)

MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFN
TSVVYKKTLFVEFTDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVITLKNMASHPVSLHAV
GVSYWKASEGAEYDDQTSQREKEDDKVFPGGSHTYVWQVLKENGPMASDPLCLTYSYLSH
VDLVKDLNSGLIGALLVCREGSLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRD
AASARAWPKMHTVNGYVNRSLPGLIGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNH
RQASLEISPITFLTAQTLLMDLGQFLLFCHISSHQHDGMEAYVKVDSCPEEPQLRMKNNE
EAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKKHPKTWVHYIAAEEEDWDYAPLVLA
PDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQHESGILGPLLYGEVGDTL
LIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIFKYKWTVTVEDGP
TKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVILFSVFDE
NRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILS
IGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRG
MTALLKVSSCDKNTGDYYEDSYEDISAYLLSKNNTTYVNRSLSQNPPVLKRHQREITRTT
LQSDQEEIDYDDTISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSS
PHVLRNRAQSGSVPQFKKVVFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIMVT
FRNQASRPYSFYSSLISYEEDQRQGAEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKA
WAYFSDVDLEKDVHSGLIGPLLVCHTNTLNPAHGRQVTVQEFALFFTIFDETKSWYFTEN
MERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPGLVMAQDQRIRWYLLSMGSNENIH
SIHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWRVECLIGEHLHAGMSTLF
LVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWSTKEPFSWIKVD
LLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGNVDSSG
IKHNIFNPPIIARYIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASS
YFTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTS
MYVKEFLISSSQDGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWV
HQIALRMEVLGCEAQDLY

Figure 54

CS01-FL-AAm12 (SEQ ID NO: 106)

MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYK
KTLFVEFTDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVVTLKNMASHPVSLHAVGVSYWKSSEGAE
YDDQTSQREKEDDKVFPGKSHTYVWQVLKENGPTASDPPCLTYSYLSHVDLVKDLNSGLIGALLVC
REGSLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGL
IGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLSCH
ISSHQHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKK
HPKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQ
HESGILGPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIF
KYKWTVTVEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVIL
FSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILS
IGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLK
VSSCDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFSQNPPVLKRHQREITRTTLQSDQEEIDYDDT
ISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSPHVLRNRAQSGSVPQFKKV
VFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQG
AEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNP
AHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPG
LVMAQDQRIRWYLLSMGSNENIHSIHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWR
VECLIGEHLHAGMSTLFLVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWS
TKEPFSWIKVDLLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGN
VDSSGIKHNIFNPPIIARYIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSY
FTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFL
ISSSQDGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCE
AQDLY

Figure 55

CS04-FL-AAm12 (SEQ ID NO: 107)

MQIELSTCFFLCLLRFCFSATRRYYLGAVELSWDYMQSDLGELPVDARFPPRVPKSFPFNTSVVYK
KTLFVEFTDHLFNIAKPRPPWMGLLGPTIQAEVYDTVVVTLKNMASHPVSLHAVGVSYWKSSEGAE
YDDQTSQREKEDDKVFPGKSHTYVWQVLKENGPTASDPPCLTYSYLSHVDLVKDLNSGLIGALLVC
REGSLAKEKTQTLHKFILLFAVFDEGKSWHSETKNSLMQDRDAASARAWPKMHTVNGYVNRSLPGL
IGCHRKSVYWHVIGMGTTPEVHSIFLEGHTFLVRNHRQASLEISPITFLTAQTLLMDLGQFLLSCH
ISSHQHDGMEAYVKVDSCPEEPQLRMKNNEEAEDYDDDLTDSEMDVVRFDDDNSPSFIQIRSVAKK
HPKTWVHYIAAEEEDWDYAPLVLAPDDRSYKSQYLNNGPQRIGRKYKKVRFMAYTDETFKTREAIQ
HESGILGPLLYGEVGDTLLIIFKNQASRPYNIYPHGITDVRPLYSRRLPKGVKHLKDFPILPGEIF
KYKWTVTVEDGPTKSDPRCLTRYYSSFVNMERDLASGLIGPLLICYKESVDQRGNQIMSDKRNVIL
FSVFDENRSWYLTENIQRFLPNPAGVQLEDPEFQASNIMHSINGYVFDSLQLSVCLHEVAYWYILS
IGAQTDFLSVFFSGYTFKHKMVYEDTLTLFPFSGETVFMSMENPGLWILGCHNSDFRNRGMTALLK
VSSCDKNTGDYYEDSYEDISAYLLSKNNAIEPRSFSQNPPVLKRHQREITRTTLQSDQEEIDYDDT
ISVEMKKEDFDIYDEDENQSPRSFQKKTRHYFIAAVERLWDYGMSSSPHVLRNRAQSGSVPQFKKV
VFQEFTDGSFTQPLYRGELNEHLGLLGPYIRAEVEDNIMVTFRNQASRPYSFYSSLISYEEDQRQG
AEPRKNFVKPNETKTYFWKVQHHMAPTKDEFDCKAWAYFSDVDLEKDVHSGLIGPLLVCHTNTLNP
AHGRQVTVQEFALFFTIFDETKSWYFTENMERNCRAPCNIQMEDPTFKENYRFHAINGYIMDTLPG
LVMAQDQRIRWYLLSMGSNENIHSIHFSGHVFTVRKKEEYKMALYNLYPGVFETVEMLPSKAGIWR
VECLIGEHLHAGMSTLFLVYSNKCQTPLGMASGHIRDFQITASGQYGQWAPKLARLHYSGSINAWS
TKEPFSWIKVDLLAPMIIHGIKTQGARQKFSSLYISQFIIMYSLDGKKWQTYRGNSTGTLMVFFGN
VDSSGIKHNIFNPPIIARYIRLHPTHYSIRSTLRMELMGCDLNSCSMPLGMESKAISDAQITASSY
FTNMFATWSPSKARLHLQGRSNAWRPQVNNPKEWLQVDFQKTMKVTGVTTQGVKSLLTSMYVKEFL
ISSSQDGHQWTLFFQNGKVKVFQGNQDSFTPVVNSLDPPLLTRYLRIHPQSWVHQIALRMEVLGCE
AQDLY

Figure 56

CS01-FL-NAm12 (SEQ ID NO: 108)

ATGCAGATTGAGCTGTCCACCTGCTTCTTTCTGTGCCTGCTGAGATTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAACTTTCTTGGGACTACATGCAGTCTGACCTGGGAGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAGTCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACACTCTTTGTGGAATTCACTGACCACCTGTTCAACATTGCAAAACCCAGACCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCGTCACCCTCAAGAACATG
GCATCCCACCCTGTGTCTCTGCATGCTGTGGGAGTCTCATACTGGAAATCCTCTGAAGGGGCTGAG
TATGATGACCAGACATCCCAGAGAGAGAAAGAGGATGACAAGGTGTTCCCTGGGAAGTCTCACACC
TATGTGTGGCAAGTCCTCAAGGAGAATGGACCCACTGCATCTGACCCACCCTGCCTGACATACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCACTGCTGGTGTGC
AGGGAAGGATCCCTGGCCAAGGAGAAAACCCAGACACTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGTCTTGGCACTCTGAAACAAAGAACTCCCTGATGCAAGACAGGGATGCTGCC
TCTGCCAGGGCATGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGATCACTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAAGTGCAC
TCCATTTTCCTGGAGGGACACACCTTCCTGGTCAGGAACCACAGACAAGCCTCTCTGGAGATCTCT
CCCATCACCTTCCTCACTGCACAGACACTGCTGATGGACCTTGGACAGTTCCTGCTGTCCTGCCAC
ATCTCTTCCCACCAGCATGATGGCATGGAAGCCTATGTCAAGGTGGACTCATGCCCTGAGGAACCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCAGATTTGATGATGACAACTCTCCATCCTTCATTCAGATCAGGTCTGTGGCAAAGAAA
CACCCCAAGACATGGGTGCACTACATTGCTGCTGAGGAAGAGGACTGGGACTATGCACCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGTCTCAGTACCTCAACAATGGCCCACAAAGAATTGGAAGA
AAGTACAAGAAAGTCAGATTCATGGCCTACACTGATGAAACCTTCAAGACAAGAGAAGCCATTCAG
CATGAGTCTGGCATTCTGGGACCACTCCTGTATGGGGAAGTGGGAGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCAGGAGACTGCCAAAAGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGAGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACAAAGTCTGACCCCAGGTGCCTCACCAGA
TACTACTCCTCTTTTGTGAACATGGAGAGAGACCTGGCATCTGGACTGATTGGACCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGAGGCAACCAGATCATGTCTGACAAGAGAAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGATCATGGTACCTGACTGAGAACATTCAGAGATTCCTGCCCAAC
CCTGCTGGGGTGCAACTGGAAGACCCTGAGTTCCAGGCAAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACTCTCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCACAAACTGACTTCCTTTCTGTCTTCTTCTCTGGATACACCTTCAAGCACAAGATGGTG
TATGAGGACACCCTGACACTCTTCCCATTCTCTGGGGAAACTGTGTTCATGAGCATGGAGAACCCT
GGACTGTGGATTCTGGGATGCCACAACTCTGACTTCAGAAACAGGGGAATGACTGCACTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACTCTTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATGCCATTGAGCCCAGAAGCTTCTCTCAGAATCCACCTGTCCTGAAGAGA
CACCAGAGAGAGATCACCAGGACAACCCTCCAGTCTGACCAGGAAGAGATTGACTATGATGACACC
ATTTCTGTGGAGATGAAGAAGGAGGACTTTGACATCTATGATGAGGACGAGAACCAGTCTCCAAGA
TCATTCCAGAAGAAGACAAGACACTACTTCATTGCTGCTGTGGAAAGACTGTGGGACTATGGCATG
TCTTCCTCTCCCCATGTCCTCAGGAACAGGGCACAGTCTGGCTCTGTGCCACAGTTCAAGAAAGTG

(Continued)

Figure 57A

GTCTTCCAGGAGTTCACTGATGGCTCATTCACCCAGCCCCTGTACAGAGGGGAACTGAATGAGCAC
CTGGGACTCCTGGGACCATACATCAGGGCTGAGGTGGAAGACAACATCATGGTGACATTCAGAAAC
CAGGCCTCCAGGCCCTACAGCTTCTACTCTTCCCTCATCAGCTATGAGGAAGACCAGAGACAAGGG
GCTGAGCCAAGAAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCAC
CACATGGCACCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCATACTTCTCTGATGTGGACCTG
GAGAAAGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCT
GCACATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAG
TCATGGTACTTCACTGAGAACATGGAGAGAAACTGCAGAGCACCATGCAACATTCAGATGGAAGAC
CCCACCTTCAAGGAGAACTACAGGTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGG
CTTGTCATGGCACAGGACCAGAGAATCAGATGGTACCTGCTTTCTATGGGATCCAATGAGAACATT
CACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGAGAAAGAAGGAGGAATACAAGATGGCCCTG
TACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGGAGG
GTGGAATGCCTCATTGGGGAGCACCTGCATGCTGGCATGTCAACCCTGTTCCTGGTCTACAGCAAC
AAGTGCCAGACACCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGC
CAGTATGGCCAGTGGGCACCCAAACTGGCCAGGCTCCACTACTCTGGCTCCATCAATGCATGGTCA
ACCAAGGAGCCATTCTCTTGGATCAAGGTGGACCTGCTGGCACCCATGATCATTCATGGCATCAAG
ACACAGGGGGCAAGACAGAAATTCTCCTCTCTGTACATCTCACAGTTCATCATCATGTACTCTCTG
GATGGCAAGAAGTGGCAGACATACAGAGGCAACTCCACTGGCACCCTCATGGTCTTCTTTGGCAAT
GTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCTCCCATCATTGCCAGATACATCAGGCTG
CACCCCACCCACTACTCAATCAGATCAACCCTCAGGATGGAACTGATGGGATGTGACCTGAACTCC
TGCTCAATGCCCCTGGGAATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCATCCTCTTAC
TTCACCAACATGTTTGCCACCTGGTCACCATCAAAAGCCAGGCTGCACCTCCAGGGAAGAAGCAAT
GCCTGGAGACCCCAGGTCAACAACCCAAAGGAATGGCTGCAAGTGGACTTCCAGAAGACAATGAAA
GTCACTGGGGGTGACAACCCAGGGGGTCAAGTCTCTGCTCACCTCAATGTATGTGAAGGAGTTCCTG
ATCTCTTCCTCACAGGATGGCCACCAGTGGACACTCTTCTTCCAGAATGGCAAAGTCAAGGTGTTC
CAGGGCAACCAGGACTCTTTCACACCTGTGGTGAACTCACTGGACCCCCCCCTCCTGACAAGATAC
CTGAGAATTCACCCCCAGTCTTGGGTCCACCAGATTGCCCTGAGAATGGAAGTCCTGGGATGTGAG
GCACAAGACCTGTACTGA

Figure 57B

CS04-FL-NAm12 (SEQ ID NO: 109)

ATGCAGATTGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGAGGTTCTGCTTCTCTGCCACCAGG
AGATACTACCTGGGGGCTGTGGAGCTTTCTTGGGACTACATGCAGTCTGACCTGGGGGAGCTGCCT
GTGGATGCCAGGTTCCCACCCAGAGTGCCCAAATCCTTCCCATTCAACACCTCTGTGGTCTACAAG
AAGACCCTCTTTGTGGAGTTCACTGACCACCTGTTCAACATTGCCAAACCCAGGCCACCCTGGATG
GGACTCCTGGGACCCACCATTCAGGCTGAGGTGTATGACACTGTGGTCGTCACCCTCAAGAACATG
GCCTCCCACCCTGTGAGCCTGCATGCTGTGGGGGTCAGCTACTGGAAGTCCTCTGAGGGGGCTGAG
TATGATGACCAGACCTCCCAGAGGGAGAAGGAGGATGACAAAGTGTTCCCTGGGAAGAGCCACACC
TATGTGTGGCAGGTCCTCAAGGAGAATGGCCCCACTGCCTCTGACCCACCCTGCCTGACCTACTCC
TACCTTTCTCATGTGGACCTGGTCAAGGACCTCAACTCTGGACTGATTGGGGCCCTGCTGGTGTGC
AGGGAGGGCTCCCTGGCCAAAGAGAAGACCCAGACCCTGCACAAGTTCATTCTCCTGTTTGCTGTC
TTTGATGAGGGCAAGAGCTGGCACTCTGAAACCAAGAACTCCCTGATGCAGGACAGGGATGCTGCC
TCTGCCAGGGCCTGGCCCAAGATGCACACTGTGAATGGCTATGTGAACAGGAGCCTGCCTGGACTC
ATTGGCTGCCACAGGAAATCTGTCTACTGGCATGTGATTGGCATGGGGACAACCCCTGAGGTGCAC
TCCATTTTCCTGGAGGGCCACACCTTCCTGGTCAGGAACCACAGACAGGCCAGCCTGGAGATCAGC
CCCATCACCTTCCTCACTGCCCAGACCCTGCTGATGGACCTCGGACAGTTCCTGCTGTCCTGCCAC
ATCAGCTCCCACCAGCATGATGGCATGGAGGCCTATGTCAAGGTGGACAGCTGCCCTGAGGAGCCA
CAGCTCAGGATGAAGAACAATGAGGAGGCTGAGGACTATGATGATGACCTGACTGACTCTGAGATG
GATGTGGTCCGCTTTGATGATGACAACAGCCCATCCTTCATTCAGATCAGGTCTGTGGCCAAGAAA
CACCCCAAGACCTGGGTGCACTACATTGCTGCTGAGGAGGAGGACTGGGACTATGCCCCACTGGTC
CTGGCCCCTGATGACAGGAGCTACAAGAGCCAGTACCTCAACAATGGCCCACAGAGGATTGGACGC
AAGTACAAGAAAGTCAGGTTCATGGCCTACACTGATGAAACCTTCAAGACCAGGGAGGCCATTCAG
CATGAGTCTGGCATCCTGGGCCCACTCCTGTATGGGGAGGTGGGGGACACCCTGCTCATCATCTTC
AAGAACCAGGCCTCCAGGCCCTACAACATCTACCCACATGGCATCACTGATGTCAGGCCCCTGTAC
AGCCGCAGGCTGCCAAAGGGGGTGAAACACCTCAAGGACTTCCCCATTCTGCCTGGGGAGATCTTC
AAGTACAAGTGGACTGTCACTGTGGAGGATGGACCAACCAAATCTGACCCCAGGTGCCTCACCAGA
TACTACTCCAGCTTTGTGAACATGGAGAGGGACCTGGCCTCTGGCCTGATTGGCCCACTGCTCATC
TGCTACAAGGAGTCTGTGGACCAGAGGGGAAACCAGATCATGTCTGACAAGAGGAATGTGATTCTG
TTCTCTGTCTTTGATGAGAACAGGAGCTGGTACCTGACTGAGAACATTCAGCGCTTCCTGCCCAAC
CCTGCTGGGGTGCAGCTGGAGGACCCTGAGTTCCAGGCCAGCAACATCATGCACTCCATCAATGGC
TATGTGTTTGACAGCCTCCAGCTTTCTGTCTGCCTGCATGAGGTGGCCTACTGGTACATTCTTTCT
ATTGGGGCCCAGACTGACTTCCTTTCTGTCTTCTTCTCTGGCTACACCTTCAAACACAAGATGGTG
TATGAGGACACCCTGACCCTCTTCCCATTCTCTGGGGAGACTGTGTTCATGAGCATGGAGAACCCT
GGCCTGTGGATTCTGGGATGCCACAACTCTGACTTCCGCAACAGGGGCATGACTGCCCTGCTCAAA
GTCTCCTCCTGTGACAAGAACACTGGGGACTACTATGAGGACAGCTATGAGGACATCTCTGCCTAC
CTGCTCAGCAAGAACAATGCCATTGAGCCCAGGAGCTTCAGCCAGAATCCACCTGTCCTGAAACGC
CACCAGAGGGAGATCACCAGGACCACCCTCCAGTCTGACCAGGAGGAGATTGACTATGATGACACC
ATTTCTGTGGAGATGAAGAAAGAGGACTTTGACATCTATGACGAGGACGAGAACCAGAGCCCAAGG
AGCTTCCAGAAGAAGACCAGGCACTACTTCATTGCTGCTGTGGAGCGCCTGTGGGACTATGGCATG
AGCTCCAGCCCCCATGTCCTCAGGAACAGGGCCCAGTCTGGCTCTGTGCCACAGTTCAAGAAAGTG
GTCTTCCAAGAGTTCACTGATGGCAGCTTCACCCAGCCCCTGTACAGAGGGGAGCTGAATGAGCAC
CTGGGACTCCTGGGCCCATACATCAGGGCTGAGGTGGAGGACAACATCATGGTGACCTTCCGCAAC

(Continued)

Figure 58A

CAGGCCTCCAGGCCCTACAGCTTCTACAGCTCCCTCATCAGCTATGAGGAGGACCAGAGGCAGGGG
GCTGAGCCACGCAAGAACTTTGTGAAACCCAATGAAACCAAGACCTACTTCTGGAAAGTCCAGCAC
CACATGGCCCCCACCAAGGATGAGTTTGACTGCAAGGCCTGGGCCTACTTCTCTGATGTGGACCTG
GAGAAGGATGTGCACTCTGGCCTGATTGGCCCACTCCTGGTCTGCCACACCAACACCCTGAACCCT
GCCCATGGAAGGCAAGTGACTGTGCAGGAGTTTGCCCTCTTCTTCACCATCTTTGATGAAACCAAG
AGCTGGTACTTCACTGAGAACATGGAGCGCAACTGCAGGGCCCCATGCAACATTCAGATGGAGGAC
CCCACCTTCAAAGAGAACTACCGCTTCCATGCCATCAATGGCTACATCATGGACACCCTGCCTGGG
CTTGTCATGGCCCAGGACCAGAGGATCAGGTGGTACCTGCTTTCTATGGGCTCCAATGAGAACATT
CACTCCATCCACTTCTCTGGGCATGTCTTCACTGTGCGCAAGAAGGAGGAGTACAAGATGGCCCTG
TACAACCTCTACCCTGGGGTCTTTGAGACTGTGGAGATGCTGCCCTCCAAAGCTGGCATCTGGAGG
GTGGAGTGCCTCATTGGGGAGCACCTGCATGCTGGCATGAGCACCCTGTTCCTGGTCTACAGCAAC
AAGTGCCAGACCCCCCTGGGAATGGCCTCTGGCCACATCAGGGACTTCCAGATCACTGCCTCTGGC
CAGTATGGCCAGTGGGCCCCCAAGCTGGCCAGGCTCCACTACTCTGGATCCATCAATGCCTGGAGC
ACCAAGGAGCCATTCAGCTGGATCAAAGTGGACCTGCTGGCCCCCATGATCATCCATGGCATCAAG
ACCCAGGGGGCCAGGCAGAAGTTCTCCAGCCTGTACATCAGCCAGTTCATCATCATGTACAGCCTG
GATGGCAAGAAATGGCAGACCTACAGAGGCAACTCCACTGGAACACTCATGGTCTTCTTTGGCAAT
GTGGACAGCTCTGGCATCAAGCACAACATCTTCAACCCCCCAATCATCGCCAGATACATCAGGCTG
CACCCCACCCACTACAGCATCCGCAGCACCCTCAGGATGGAGCTGATGGGCTGTGACCTGAACTCC
TGCAGCATGCCCCTGGGCATGGAGAGCAAGGCCATTTCTGATGCCCAGATCACTGCCTCCAGCTAC
TTCACCAACATGTTTGCCACCTGGAGCCCAAGCAAGGCCAGGCTGCACCTCCAGGGAAGGAGCAAT
GCCTGGAGGCCCCAGGTCAACAACCCAAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAG
GTCACTGGGGTGACCACCCAGGGGGTCAAGAGCCTGCTCACCAGCATGTATGTGAAGGAGTTCCTG
ATCAGCTCCAGCCAGGATGGCCACCAGTGGACCCTCTTCTTCCAGAATGGCAAGGTCAAGGTGTTC
CAGGGCAACCAGGACAGCTTCACCCCTGTGGTGAACAGCCTGGACCCCCCCCTCCTGACCAGATAC
CTGAGGATTCACCCCCAGAGCTGGGTCCACCAGATTGCCCTGAGGATGGAGGTCCTGGGATGTGAG
GCCCAGGACCTGTACTGA

Figure 58B

VIRAL VECTORS ENCODING RECOMBINANT FVIII VARIANTS WITH INCREASED EXPRESSION FOR GENE THERAPY OF HEMOPHILIA A

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. application Ser. No. 15/349,930, filed Nov. 11, 2016, which claims priority to U.S. Provisional Patent Application No. 62/255,317, filed Nov. 13, 2015, the content of which are hereby incorporated by reference in its entirety for all purposes.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Nov. 9, 2016, is named 008073_5107_US01_Sequence_Listing.txt and is 345 KB bytes in size.

BACKGROUND OF THE DISCLOSURE

[0003] Blood coagulation proceeds through a complex and dynamic biological pathway of interdependent biochemical reactions, referred to as the coagulation cascade. Coagulation Factor VIII (FVIII) is a key component in the cascade. Factor VIII is recruited to bleeding sites, and forms a Xase complex with activated Factor IX (FIXa) and Factor X (FX). The Xase complex activates FX, which in turn activates prothrombin to thrombin, which then activates other components in the coagulation cascade to generate a stable clot (reviewed in Saenko et al., *Trends Cardiovasc. Med.,* 9:185-192 (1999); Lenting et al., *Blood,* 92:3983-3996 (1998)).

[0004] Hemophilia A is a congenital X-linked bleeding disorder characterized by a deficiency in Factor VIII activity. Diminished Factor VIII activity inhibits a positive feedback loop in the coagulation cascade. This causes incomplete coagulation, which manifests as bleeding episodes with increased duration, extensive bruising, spontaneous oral and nasal bleeding, joint stiffness and chronic pain, and possibly internal bleeding and anemia in severe cases (Zhang et al., *Clinic. Rev. Allerg. Immunol.,* 37:114-124 (2009)).

[0005] Conventionally, hemophilia A is treated by Factor VIII replacement therapy, which consists of administering Factor VIII protein (e.g., plasma-derived or recombinantly-produced Factor VIII) to an individual with hemophilia A. Factor VIII is administered prophylactically to prevent or reduce frequency of bleeding episodes, in response to an acute bleeding episode, and/or perioperatively to manage bleeding during surgery. However, there are several undesirable features of Factor VIII replacement therapy.

[0006] First, Factor VIII replacement therapy is used to treat or manage hemophilia A, but does not cure the underlying Factor VIII deficiency. Because of this, individuals with hemophilia A require Factor VIII replacement therapy for the duration of their lives. Continuous treatment is expensive and requires the individual to maintain strict compliance, as missing only a few prophylactic doses can have serious consequences for individuals with severe hemophilia A.

[0007] Second, because Factor VIII has a relatively short half-life in vivo, conventional prophylactic Factor VIII replacement therapy requires administration every second or third day. This places a burden on the individual to maintain compliance throughout their life. While third generation "long-acting" Factor VIII drugs may reduce the frequency of administration, prophylactic Factor FVIII replacement therapy with these drugs still requires monthly, weekly, or more frequent administration in perpetuity. For example, prophylactic treatment with ELOCTATE™ [Antihemophilic Factor (Recombinant), Fc Fusion Protein] requires administration every three to five days (ELOCTATE™ Prescribing Information, Biogen Idec Inc., (2015)). Moreover, the long-term effects of chemically modified biologics (e.g., pegylated polypeptides) are not yet fully understood.

[0008] Third, between 15% and 30% of all individuals receiving Factor VIII replacement therapy form anti-Factor VIII inhibitor antibodies, rendering the therapy inefficient. Factor VIII bypass therapy (e.g., administration of plasma-derived or recombinantly-produced prothrombin complex concentrates) can be used to treat hemophilia in individuals that form inhibitor antibodies. However, Factor VIII bypass therapy is less effective than Factor VIII replacement therapy (Mannucci P. M., J Thromb Haemost., 1(7):1349-55 (2003)) and may be associated with an increased risk of cardiovascular complication (Luu and Ewenstein, Haemophilia, 10 Suppl. 2:10-16 (2004)).

[0009] Somatic gene therapy holds great promise for the treatment of hemophilia A because it would remedy the underlying under-expression functional Factor VIII activity (e.g., due to missense or nonsense mutations), rather than provide a one-time dose of Factor VIII activity to the individual. Because of this difference in the mechanism of action, as compared to Factor VIII replacement therapy, one-time administration of a Factor VIII gene therapy vector may provide an individual with Factor VIII for several years, reducing the cost of treatment and eliminating the need for continued patient compliance.

[0010] Coagulation Factor IX (FIX) gene therapy has been used effectively to treat individuals with hemophilia B, a related blood coagulation condition characterized by diminished Factor IX activity (Manno C. S., et al., Nat Med., 12(3):342-47 (2006)). However, Factor VIII gene therapy presents several unique challenges. For example, the full-length, wild-type Factor VIII polypeptide (2351 amino acids; UniProt accession number P00451) is five times larger than the full-length, wild-type Factor IX polypeptide (461 amino acids; UniProt accession number P00740). As such, the coding sequence of wild-type Factor VIII is 7053 base pairs, which is too large to be packaged in conventional AAV gene therapy vectors. Further, reported recombinant expression of B-domain deleted variants of Factor VIII (BDD-FVIII) has been poor. As such, several groups have attempted to alter the codon usage of BDD-FVIII constructs, with limited success.

BRIEF SUMMARY OF DISCLOSURE

[0011] Accordingly, there is a need for Factor VIII variants whose coding sequences are more efficiently packaged into, and delivered via, gene therapy vectors. There is also a need for synthetic, codon-altered nucleic acids which express Factor VIII more efficiently. Such Factor VIII variants and codon-altered nucleic acids allow for improved treatment of Factor VIII deficiencies (e.g., hemophilia A). The above deficiencies and other problems associated with the treat-

ment of Factor VIII deficiencies (e.g., hemophilia A) are reduced or eliminated by the disclosed codon-altered Factor VIII variants.

[0012] In accordance with some embodiments, the present disclosure provides nucleic acids encoding Factor VIII variants that have high sequence identity to the disclosed codon-altered sequences of the Factor VIII heavy chain (e.g., CS01-HC-NA, CS04-HC-NA, or CS23-HC-NA) and light chain (CS01-LC-NA, CS04-LC-NA, or CS23-LC-NA). In some embodiments, these nucleic acids further include a sequence encoding a linker sequence that replaces the native Factor VIII B-domain (e.g., a linker sequences comprising a furin cleavage site), between the sequences coding for the Factor VIII heavy and light chains.

[0013] In one aspect, the disclosure provides a polynucleotide including a nucleotide sequence encoding a Factor VIII polypeptide. The Factor VIII polypeptide includes a light chain, a heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having at least 95% identity to CS04-HC-NA (SEQ ID NO: 3). The light chain of the Factor FVIII polypeptide is encoded by a second nucleotide sequence having at least 95% identity to CS04-LC-NA (SEQ ID NO: 4). The polypeptide linker comprises a furin cleavage site.

[0014] In one embodiment of the polynucleotides described above, the polypeptide linker is encoded by a third nucleotide sequence having at least 95% identity to BDLO04 (SEQ ID NO: 6).

[0015] In one aspect, the disclosure provides a polynucleotide including a nucleotide sequence encoding a Factor VIII polypeptide. The Factor VIII polypeptide includes a light chain, a heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having at least 95% identity to CS01-HC-NA (SEQ ID NO: 24). The light chain of the Factor FVIII polypeptide is encoded by a second nucleotide sequence having at least 95% identity to CS01-LC-NA (SEQ ID NO: 25). The polypeptide linker comprises a furin cleavage site.

[0016] In one embodiment of the polynucleotides described above, the polypeptide linker is encoded by a third nucleotide sequence having at least 95% identity to BDLO01 (SEQ ID NO: 5).

[0017] In one aspect, the disclosure provides a polynucleotide including a nucleotide sequence encoding a Factor VIII polypeptide. The Factor VIII polypeptide includes a light chain, a heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having at least 95% identity to CS23-HC-NA (SEQ ID NO: 22). The light chain of the Factor FVIII polypeptide is encoded by a second nucleotide sequence having at least 95% identity to CS23-LC-NA (SEQ ID NO: 23). The polypeptide linker comprises a furin cleavage site.

[0018] In one embodiment of the polynucleotides described above, the polypeptide linker is encoded by a third nucleotide sequence having at least 95% identity to BDLO23 (SEQ ID NO: 7).

[0019] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide has at least 96% identity to the respective heavy chain sequence (e.g., CS04-HC-NA (SEQ ID NO: 3), CS01-HC-NA (SEQ ID NO: 24), or CS23-HC-NA (SEQ ID NO: 22)), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide has at least 96% identity to the respective light chain sequence (e.g., CS04-LC-NA (SEQ ID NO: 4), CS01-LC-NA (SEQ ID NO: 25), or CS23-LC-NA (SEQ ID NO: 23)).

[0020] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide has at least 97% identity to the respective heavy chain sequence (e.g., CS04-HC-NA (SEQ ID NO: 3), CS01-HC-NA (SEQ ID NO: 24), or CS23-HC-NA (SEQ ID NO: 22)), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide has at least 97% identity to the respective light chain sequence (e.g., CS04-LC-NA (SEQ ID NO: 4), CS01-LC-NA (SEQ ID NO: 25), or CS23-LC-NA (SEQ ID NO: 23)).

[0021] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide has at least 98% identity to the respective heavy chain sequence (e.g., CS04-HC-NA (SEQ ID NO: 3), CS01-HC-NA (SEQ ID NO: 24), or CS23-HC-NA (SEQ ID NO: 22)), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide has at least 98% identity to the respective light chain sequence (e.g., CS04-LC-NA (SEQ ID NO: 4), CS01-LC-NA (SEQ ID NO: 25), or CS23-LC-NA (SEQ ID NO: 23)).

[0022] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide has at least 99% identity to the respective heavy chain sequence (e.g., CS04-HC-NA (SEQ ID NO: 3), CS01-HC-NA (SEQ ID NO: 24), or CS23-HC-NA (SEQ ID NO: 22)), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide has at least 99% identity to the respective light chain sequence (e.g., CS04-LC-NA (SEQ ID NO: 4), CS01-LC-NA (SEQ ID NO: 25), or CS23-LC-NA (SEQ ID NO: 23)).

[0023] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide has at least 99.5% identity to the respective heavy chain sequence (e.g., CS04-HC-NA (SEQ ID NO: 3), CS01-HC-NA (SEQ ID NO: 24), or CS23-HC-NA (SEQ ID NO: 22)), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide has at least 99.5% identity to the respective light chain sequence (e.g., CS04-LC-NA (SEQ ID NO: 4), CS01-LC-NA (SEQ ID NO: 25), or CS23-LC-NA (SEQ ID NO: 23)).

[0024] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide has at least 99.9% identity to the respective heavy chain sequence (e.g., CS04-HC-NA (SEQ ID NO: 3), CS01-HC-NA (SEQ ID NO: 24), or CS23-HC-NA (SEQ ID NO: 22)), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide has at least 99.9% identity to the respective light chain sequence (e.g., CS04-LC-NA (SEQ ID NO: 4), CS01-LC-NA (SEQ ID NO: 25), or CS23-LC-NA (SEQ ID NO: 23)).

[0025] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide is CS04-HC-NA (SEQ ID NO: 3), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide is CS04-LC-NA (SEQ ID NO: 4).

[0026] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide is CS01-HC-NA (SEQ ID NO: 24), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide is CS01-LC-NA (SEQ ID NO: 25).

[0027] In one embodiment of the polynucleotides described above, the first nucleotide sequence encoding the heavy chain of the Factor VIII polypeptide is CS23-HC-NA (SEQ ID NO: 22), and the second nucleotide sequence encoding the light chain of the Factor FVIII polypeptide is CS23-LC-NA (SEQ ID NO: 23).

[0028] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS04-FL-NA, wherein the polynucleotide encodes a Factor VIII polypeptide.

[0029] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS01-FL-NA, wherein the polynucleotide encodes a Factor VIII polypeptide.

[0030] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS23-FL-NA, wherein the polynucleotide encodes a Factor VIII polypeptide.

[0031] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 96% identity to the respective full-length polynucleotide sequence (e.g., CS04-FL-NA (SEQ ID NO: 1), CS01-FL-NA (SEQ ID NO: 13), or CS23-FL-NA (SEQ ID NO: 20)).

[0032] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 97% identity to the respective full-length polynucleotide sequence (e.g., CS04-FL-NA (SEQ ID NO: 1), CS01-FL-NA (SEQ ID NO: 13), or CS23-FL-NA (SEQ ID NO: 20)).

[0033] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 98% identity to the respective full-length polynucleotide sequence (e.g., CS04-FL-NA (SEQ ID NO: 1), CS01-FL-NA (SEQ ID NO: 13), or CS23-FL-NA (SEQ ID NO: 20)).

[0034] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99% identity to the respective full-length polynucleotide sequence (e.g., CS04-FL-NA (SEQ ID NO: 1), CS01-FL-NA (SEQ ID NO: 13), or CS23-FL-NA (SEQ ID NO: 20)).

[0035] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99.5% identity to the respective full-length polynucleotide sequence (e.g., CS04-FL-NA (SEQ ID NO: 1), CS01-FL-NA (SEQ ID NO: 13), or CS23-FL-NA (SEQ ID NO: 20)).

[0036] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99.9% identity to the respective full-length polynucleotide sequence (e.g., CS04-FL-NA (SEQ ID NO: 1), CS01-FL-NA (SEQ ID NO: 13), or CS23-FL-NA (SEQ ID NO: 20)).

[0037] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS04-FL-NA (SEQ ID NO: 1).

[0038] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS01-FL-NA (SEQ ID NO: 13).

[0039] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS23-FL-NA (SEQ ID NO: 20).

[0040] In one embodiment of the polynucleotides described above, the polynucleotide encodes a Factor VIII polypeptide comprising an amino acid sequence having at least 95% identity to CS04-FL-AA (SEQ ID NO: 2).

[0041] In one embodiment of the polynucleotides described above, the polynucleotide encodes a Factor VIII polypeptide comprising an amino acid sequence having at least 96% identity to CS04-FL-AA (SEQ ID NO: 2).

[0042] In one embodiment of the polynucleotides described above, the polynucleotide encodes a Factor VIII polypeptide comprising an amino acid sequence having at least 97% identity to CS04-FL-AA (SEQ ID NO: 2).

[0043] In one embodiment of the polynucleotides described above, the polynucleotide encodes a Factor VIII polypeptide comprising an amino acid sequence having at least 98% identity to CS04-FL-AA (SEQ ID NO: 2).

[0044] In one embodiment of the polynucleotides described above, the polynucleotide encodes a Factor VIII polypeptide comprising an amino acid sequence having at least 99% identity to CS04-FL-AA (SEQ ID NO: 2).

[0045] In one embodiment of the polynucleotides described above, the polynucleotide encodes a Factor VIII polypeptide comprising an amino acid sequence having at least 99.5% identity to CS04-FL-AA (SEQ ID NO: 2).

[0046] In one embodiment of the polynucleotides described above, the polynucleotide encodes a Factor VIII polypeptide comprising an amino acid sequence having at least 99.9% identity to CS04-FL-AA (SEQ ID NO: 2).

[0047] In one embodiment of the polynucleotides described above, the polynucleotide encodes a Factor VIII polypeptide comprising the amino acid sequence of CS04-FL-AA (SEQ ID NO: 2).

[0048] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS04-SC1-NA (SEQ ID NO: 9), wherein the polynucleotide encodes a single-chain Factor VIII polypeptide.

[0049] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS04-SC2-NA (SEQ ID NO: 11), wherein the polynucleotide encodes a single-chain Factor VIII polypeptide.

[0050] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS01-SC1-NA (SEQ ID NO: 26), wherein the polynucleotide encodes a single-chain Factor VIII polypeptide.

[0051] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS01-SC2-NA (SEQ ID NO: 27), wherein the polynucleotide encodes a single-chain Factor VIII polypeptide.

[0052] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS23-SC1-NA (SEQ ID NO: 28), wherein the polynucleotide encodes a single-chain Factor VIII polypeptide.

[0053] In one aspect, the disclosure provides a polynucleotide comprising a nucleotide sequence having at least 95% identity to CS23-SC2-NA (SEQ ID NO: 29), wherein the polynucleotide encodes a single-chain Factor VIII polypeptide.

[0054] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 96% identity to the respective full-length polynucleotide sequence (e.g., CS04-SC1-NA (SEQ ID NO: 9), CS04-SC2-NA (SEQ ID NO: 11), CS01-SC1-NA (SEQ ID NO: 26), CS01-SC2-NA (SEQ ID NO: 27), CS23-SC1-NA (SEQ ID NO: 28), or CS23-SC2-NA (SEQ ID NO: 29)).

[0055] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 97% identity to the respective full-length polynucleotide sequence (e.g., CS04-SC1-NA (SEQ ID NO: 9), CS04-SC2-NA (SEQ ID NO: 11), CS01-SC1-NA (SEQ ID NO: 26), CS01-SC2-NA (SEQ ID NO: 27), CS23-SC1-NA (SEQ ID NO: 28), or CS23-SC2-NA (SEQ ID NO: 29)).

[0056] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 98% identity to the respective full-length polynucleotide sequence (e.g., CS04-SC1-NA (SEQ ID NO: 9), CS04-SC2-NA (SEQ ID NO: 11), CS01-SC1-NA (SEQ ID NO: 26), CS01-SC2-NA (SEQ ID NO: 27), CS23-SC1-NA (SEQ ID NO: 28), or CS23-SC2-NA (SEQ ID NO: 29)).

[0057] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99% identity to the respective full-length polynucleotide sequence (e.g., CS04-SC1-NA (SEQ ID NO: 9), CS04-SC2-NA (SEQ ID NO: 11), CS01-SC1-NA (SEQ ID NO: 26), CS01-SC2-NA (SEQ ID NO: 27), CS23-SC1-NA (SEQ ID NO: 28), or CS23-SC2-NA (SEQ ID NO: 29)).

[0058] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99.5% identity to the respective full-length polynucleotide sequence (e.g., CS04-SC1-NA (SEQ ID NO: 9), CS04-SC2-NA (SEQ ID NO: 11), CS01-SC1-NA (SEQ ID NO: 26), CS01-SC2-NA (SEQ ID NO: 27), CS23-SC1-NA (SEQ ID NO: 28), or CS23-SC2-NA (SEQ ID NO: 29)).

[0059] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99.9% identity to the respective full-length polynucleotide sequence (e.g., CS04-SC1-NA (SEQ ID NO: 9), CS04-SC2-NA (SEQ ID NO: 11), CS01-SC1-NA (SEQ ID NO: 26), CS01-SC2-NA (SEQ ID NO: 27), CS23-SC1-NA (SEQ ID NO: 28), or CS23-SC2-NA (SEQ ID NO: 29)).

[0060] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS04-SC1-NA (SEQ ID NO: 9).

[0061] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS04-SC2-NA (SEQ ID NO: 11).

[0062] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS01-SC1-NA (SEQ ID NO: 26).

[0063] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS01-SC2-NA (SEQ ID NO: 27).

[0064] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS23-SC1-NA (SEQ ID NO: 28).

[0065] In one embodiment of the polynucleotides described above, the nucleotide sequence is CS23-SC2-NA (SEQ ID NO: 29).

[0066] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 95% identity to a sequence selected from the group consisting of CS01-FL-NA, CS01-HC-NA, CS01-LC-NA, CS04-FL-NA, CS04-HC-NA, CS04-LC-NA, CS23-FL-NA, CS23-HC-NA, CS23-LC-NA, CS01m1-FL-NA, CS01m2-FL-NA, CS01m3-FL-NA, CS01m4-FL-NA, CS01m12-FL-NA, CS01m13-FL-NA, CS01m23-FL-NA, CS01m24-FL-NA, CS01m34-FL-NA, CS01m123-FL-NA, CS01m234-FL-NA, CS04m1-FL-NA, CS04m2-FL-NA, CS04m3-FL-NA, CS04m4-FL-NA, CS04m12-FL-NA, CS04m13-FL-NA, CS04m23-FL-NA, CS04m24-FL-NA, CS04m34-FL-NA, CS04m123-FL-NA, CS04m234-FL-NA, CS23m1-FL-NA, CS23m2-FL-NA, CS23m3-FL-NA, CS23m4-FL-NA, CS23m12-FL-NA, CS23m13-FL-NA, CS23m23-FL-NA, CS23m24-FL-NA, CS23m34-FL-NA, CS23m123-FL-NA, CS23m234-FL-NA, CS01-SC1-NA, CS04-SC1-NA, CS23-SC1-NA, CS01m1-SC1-NA, CS01m2-SC1-NA, CS01m3-SC1-NA, CS01m4-SC1-NA, CS01m12-SC1-NA, CS01m13-SC1-NA, CS01m23-SC1-NA, CS01m24-SC1-NA, CS01m34-SC1-NA, CS01m123-SC1-NA, CS01m234-SC1-NA, CS04m1-SC1-NA, CS04m2-SC1-NA, CS04m3-SC1-NA, CS04m4-SC1-NA, CS04m12-SC1-NA, CS04m13-SC1-NA, CS04m23-SC1-NA, CS04m24-SC1-NA, CS04m34-SC1-NA, CS04m123-SC1-NA, CS04m234-SC1-NA, CS23m1-SC1-NA, CS23m2-SC1-NA, CS23m3-SC1-NA, CS23m4-SC1-NA, CS23m12-SC1-NA, CS23m13-SC1-NA, CS23m23-SC1-NA, CS23m24-SC1-NA, CS23m34-SC1-NA, CS23m123-SC1-NA, CS23m234-SC1-NA, CS01-SC2-NA, CS04-SC2-NA, CS23-SC2-NA, CS01m1-SC2-NA, CS01m2-SC2-NA, CS01m3-SC2-NA, CS01m4-SC2-NA, CS01m12-SC2-NA, CS01m13-SC2-NA, CS01m23-SC2-NA, CS01m24-SC2-NA, CS01m34-SC2-NA, CS01m123-SC2-NA, CS01m234-SC2-NA, CS04m1-SC2-NA, CS04m2-SC2-NA, CS04m3-SC2-NA, CS04m4-SC2-NA, CS04m12-SC2-NA, CS04m13-SC2-NA, CS04m23-SC2-NA, CS04m24-SC2-NA, CS04m34-SC2-NA, CS04m123-SC2-NA, CS04m234-SC2-NA, CS23m1-SC2-NA, CS23m2-SC2-NA, CS23m3-SC2-NA, CS23m4-SC2-NA, CS23m12-SC2-NA, CS23m13-SC2-NA, CS23m23-SC2-NA, CS23m24-SC2-NA, CS23m34-SC2-NA, CS23m123-SC2-NA, and CS23m234-SC2-NA.

[0067] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 96% identity to a sequence selected from the group consisting of CS01-FL-NA, CS01-HC-NA, CS01-LC-NA, CS04-FL-NA, CS04-HC-NA, CS04-LC-NA, CS23-FL-NA, CS23-HC-NA, CS23-LC-NA, CS01m1-FL-NA, CS01m2-FL-NA, CS01m3-FL-NA, CS01m4-FL-NA, CS01m12-FL-NA, CS01m13-FL-NA, CS01m23-FL-NA, CS01m24-FL-NA, CS01m34-FL-NA, CS01m123-FL-NA, CS01m234-FL-NA, CS04m1-FL-NA, CS04m2-FL-NA, CS04m3-FL-NA, CS04m4-FL-NA, CS04m12-FL-NA, CS04m13-FL-NA, CS04m23-FL-NA, CS04m24-FL-NA, CS04m34-FL-NA, CS04m123-FL-NA, CS04m234-FL-NA, CS23m1-FL-NA, CS23m2-FL-NA, CS23m3-FL-NA, CS23m4-FL-NA, CS23m12-FL-NA, CS23m13-FL-NA, CS23m23-FL-NA, CS23m24-FL-NA, CS23m34-FL-NA, CS23m123-FL-NA, CS23m234-FL-NA, CS01-SC1-NA, CS04-SC1-NA, CS23-SC1-NA, CS01m1-SC1-NA, CS01m2-SC1-NA, CS01m3-SC1-NA, CS01m4-SC1-NA, CS01m12-SC1-NA,

CS01m13-SC1-NA, CS01m23-SC1-NA, CS01m24-SC1-NA, CS01m34-SC1-NA, CS01m123-SC1-NA, CS01m234-SC1-NA, CS04m1-SC1-NA, CS04m2-SC1-NA, CS04m3-SC1-NA, CS04m4-SC1-NA, CS04m12-SC1-NA, CS04m13-SC1-NA, CS04m23-SC1-NA, CS04m24-SC1-NA, CS04m34-SC1-NA, CS04m123-SC1-NA, CS04m234-SC1-NA, CS23m1-SC1-NA, CS23m2-SC1-NA, CS23m3-SC1-NA, CS23m4-SC1-NA, CS23m12-SC1-NA, CS23m13-SC1-NA, CS23m23-SC1-NA, CS23m24-SC1-NA, CS23m34-SC1-NA, CS23m123-SC1-NA, CS23m234-SC1-NA, CS01-SC2-NA, CS04-SC2-NA, CS23-SC2-NA, CS01m1-SC2-NA, CS01m2-SC2-NA, CS01m3-SC2-NA, CS01m4-SC2-NA, CS01m12-SC2-NA, CS01m13-SC2-NA, CS01m23-SC2-NA, CS01m24-SC2-NA, CS01m34-SC2-NA, CS01m123-SC2-NA, CS01m234-SC2-NA, CS04m1-SC2-NA, CS04m2-SC2-NA, CS04m3-SC2-NA, CS04m4-SC2-NA, CS04m12-SC2-NA, CS04m13-SC2-NA, CS04m23-SC2-NA, CS04m24-SC2-NA, CS04m34-SC2-NA, CS04m123-SC2-NA, CS04m234-SC2-NA, CS23m1-SC2-NA, CS23m2-SC2-NA, CS23m3-SC2-NA, CS23m4-SC2-NA, CS23m12-SC2-NA, CS23m13-SC2-NA, CS23m23-SC2-NA, CS23m24-SC2-NA, CS23m34-SC2-NA, CS23m123-SC2-NA, and CS23m234-SC2-NA.

[0068] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 97% identity to a sequence selected from the group consisting of CS01-FL-NA, CS01-HC-NA, CS01-LC-NA, CS04-FL-NA, CS04-HC-NA, CS04-LC-NA, CS23-FL-NA, CS23-HC-NA, CS23-LC-NA, CS01m1-FL-NA, CS01m2-FL-NA, CS01m3-FL-NA, CS01m4-FL-NA, CS01m12-FL-NA, CS01m13-FL-NA, CS01m23-FL-NA, CS01m24-FL-NA, CS01m34-FL-NA, CS01m123-FL-NA, CS01m234-FL-NA, CS04m1-FL-NA, CS04m2-FL-NA, CS04m3-FL-NA, CS04m4-FL-NA, CS04m12-FL-NA, CS04m13-FL-NA, CS04m23-FL-NA, CS04m24-FL-NA, CS04m34-FL-NA, CS04m123-FL-NA, CS04m234-FL-NA, CS23m1-FL-NA, CS23m2-FL-NA, CS23m3-FL-NA, CS23m4-FL-NA, CS23m12-FL-NA, CS23m13-FL-NA, CS23m23-FL-NA, CS23m24-FL-NA, CS23m34-FL-NA, CS23m123-FL-NA, CS23m234-FL-NA, CS01-SC1-NA, CS04-SC1-NA, CS23-SC1-NA, CS01m1-SC1-NA, CS01m2-SC1-NA, CS01m3-SC1-NA, CS01m4-SC1-NA, CS01m12-SC1-NA, CS01m13-SC1-NA, CS01m23-SC1-NA, CS01m24-SC1-NA, CS01m34-SC1-NA, CS01m123-SC1-NA, CS01m234-SC1-NA, CS04m1-SC1-NA, CS04m2-SC1-NA, CS04m3-SC1-NA, CS04m4-SC1-NA, CS04m12-SC1-NA, CS04m13-SC1-NA, CS04m23-SC1-NA, CS04m24-SC1-NA, CS04m34-SC1-NA, CS04m123-SC1-NA, CS04m234-SC1-NA, CS23m1-SC1-NA, CS23m2-SC1-NA, CS23m3-SC1-NA, CS23m4-SC1-NA, CS23m12-SC1-NA, CS23m13-SC1-NA, CS23m23-SC1-NA, CS23m24-SC1-NA, CS23m34-SC1-NA, CS23m123-SC1-NA, CS23m234-SC1-NA, CS01-SC2-NA, CS04-SC2-NA, CS23-SC2-NA, CS01m1-SC2-NA, CS01m2-SC2-NA, CS01m3-SC2-NA, CS01m4-SC2-NA, CS01m12-SC2-NA, CS01m13-SC2-NA, CS01m23-SC2-NA, CS01m24-SC2-NA, CS01m34-SC2-NA, CS01m123-SC2-NA, CS01m234-SC2-NA, CS04m1-SC2-NA, CS04m2-SC2-NA, CS04m3-SC2-NA, CS04m4-SC2-NA, CS04m12-SC2-NA, CS04m13-SC2-NA, CS04m23-SC2-NA, CS04m24-SC2-NA, CS04m34-SC2-NA, CS04m123-SC2-NA, CS04m234-SC2-NA, CS23m1-SC2-NA, CS23m2-SC2-NA, CS23m3-SC2-NA, CS23m4-SC2-NA, CS23m12-SC2-NA, CS23m13-SC2-NA, CS23m23-SC2-NA, CS23m24-SC2-NA, CS23m34-SC2-NA, CS23m123-SC2-NA, and CS23m234-SC2-NA.

[0069] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 98% identity to a sequence selected from the group consisting of CS01-FL-NA, CS01-HC-NA, CS01-LC-NA, CS04-FL-NA, CS04-HC-NA, CS04-LC-NA, CS23-FL-NA, CS23-HC-NA, CS23-LC-NA, CS01m1-FL-NA, CS01m2-FL-NA, CS01m3-FL-NA, CS01m4-FL-NA, CS01m12-FL-NA, CS01m13-FL-NA, CS01m23-FL-NA, CS01m24-FL-NA, CS01m34-FL-NA, CS01m123-FL-NA, CS01m234-FL-NA, CS04m1-FL-NA, CS04m2-FL-NA, CS04m3-FL-NA, CS04m4-FL-NA, CS04m12-FL-NA, CS04m13-FL-NA, CS04m23-FL-NA, CS04m24-FL-NA, CS04m34-FL-NA, CS04m123-FL-NA, CS04m234-FL-NA, CS23m1-FL-NA, CS23m2-FL-NA, CS23m3-FL-NA, CS23m4-FL-NA, CS23m12-FL-NA, CS23m13-FL-NA, CS23m23-FL-NA, CS23m24-FL-NA, CS23m34-FL-NA, CS23m123-FL-NA, CS23m234-FL-NA, CS01-SC1-NA, CS04-SC1-NA, CS23-SC1-NA, CS01m1-SC1-NA, CS01m2-SC1-NA, CS01m3-SC1-NA, CS01m4-SC1-NA, CS01m12-SC1-NA, CS01m13-SC1-NA, CS01m23-SC1-NA, CS01m24-SC1-NA, CS01m34-SC1-NA, CS01m123-SC1-NA, CS01m234-SC1-NA, CS04m1-SC1-NA, CS04m2-SC1-NA, CS04m3-SC1-NA, CS04m4-SC1-NA, CS04m12-SC1-NA, CS04m13-SC1-NA, CS04m23-SC1-NA, CS04m24-SC1-NA, CS04m34-SC1-NA, CS04m123-SC1-NA, CS04m234-SC1-NA, CS23m1-SC1-NA, CS23m2-SC1-NA, CS23m3-SC1-NA, CS23m4-SC1-NA, CS23m12-SC1-NA, CS23m13-SC1-NA, CS23m23-SC1-NA, CS23m24-SC1-NA, CS23m34-SC1-NA, CS23m123-SC1-NA, CS23m234-SC1-NA, CS01-SC2-NA, CS04-SC2-NA, CS23-SC2-NA, CS01m1-SC2-NA, CS01m2-SC2-NA, CS01m3-SC2-NA, CS01m4-SC2-NA, CS01m12-SC2-NA, CS01m13-SC2-NA, CS01m23-SC2-NA, CS01m24-SC2-NA, CS01m34-SC2-NA, CS01m123-SC2-NA, CS01m234-SC2-NA, CS04m1-SC2-NA, CS04m2-SC2-NA, CS04m3-SC2-NA, CS04m4-SC2-NA, CS04m12-SC2-NA, CS04m13-SC2-NA, CS04m23-SC2-NA, CS04m24-SC2-NA, CS04m34-SC2-NA, CS04m123-SC2-NA, CS04m234-SC2-NA, CS23m1-SC2-NA, CS23m2-SC2-NA, CS23m3-SC2-NA, CS23m4-SC2-NA, CS23m12-SC2-NA, CS23m13-SC2-NA, CS23m23-SC2-NA, CS23m24-SC2-NA, CS23m34-SC2-NA, CS23m123-SC2-NA, and CS23m234-SC2-NA.

[0070] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99% identity to a sequence selected from the group consisting of CS01-FL-NA, CS01-HC-NA, CS01-LC-NA, CS04-FL-NA, CS04-HC-NA, CS04-LC-NA, CS23-FL-NA, CS23-HC-NA, CS23-LC-NA, CS01m1-FL-NA, CS01m2-FL-NA, CS01m3-FL-NA, CS01m4-FL-NA, CS01m12-FL-NA, CS01m13-FL-NA, CS01m23-FL-NA, CS01m24-FL-NA, CS01m34-FL-NA, CS01m123-FL-NA, CS01m234-FL-NA, CS04m1-FL-NA, CS04m2-FL-NA, CS04m3-FL-NA, CS04m4-FL-NA, CS04m12-FL-NA, CS04m13-FL-NA, CS04m23-FL-NA, CS04m24-FL-NA, CS04m34-FL-NA, CS04m123-FL-NA, CS04m234-FL-NA, CS23m1-FL-NA, CS23m2-FL-NA, CS23m3-FL-NA, CS23m4-FL-NA, CS23m12-FL-NA, CS23m13-FL-NA, CS23m23-FL-NA, CS23m24-FL-NA, CS23m34-FL-NA, CS23m123-FL-NA, CS23m234-FL-NA, CS01-SC1-NA, CS04-SC1-NA, CS23-SC1-NA, CS01m1-SC1-NA, CS01m2-SC1-NA, CS01m3-SC1-NA, CS01m4-SC1-NA, CS01m12-SC1-NA, CS01m13-SC1-NA, CS01m23-SC1-NA, CS01m24-SC1-

NA, CS01m34-SC1-NA, CS01m123-SC1-NA, CS01m234-SC1-NA, CS04m1-SC1-NA, CS04m2-SC1-NA, CS04m3-SC1-NA, CS04m4-SC1-NA, CS04m12-SC1-NA, CS04m13-SC1-NA, CS04m23-SC1-NA, CS04m24-SC1-NA, CS04m34-SC1-NA, CS04m123-SC1-NA, CS04m234-SC1-NA, CS23m1-SC1-NA, CS23m2-SC1-NA, CS23m3-SC1-NA, CS23m4-SC1-NA, CS23m12-SC1-NA, CS23m13-SC1-NA, CS23m23-SC1-NA, CS23m24-SC1-NA, CS23m34-SC1-NA, CS23m123-SC1-NA, CS23m234-SC1-NA, CS01-SC2-NA, CS04-SC2-NA, CS23-SC2-NA, CS01m1-SC2-NA, CS01m2-SC2-NA, CS01m3-SC2-NA, CS01m4-SC2-NA, CS01m12-SC2-NA, CS01m13-SC2-NA, CS01m23-SC2-NA, CS01m24-SC2-NA, CS01m34-SC2-NA, CS01m123-SC2-NA, CS01m234-SC2-NA, CS04m1-SC2-NA, CS04m2-SC2-NA, CS04m3-SC2-NA, CS04m4-SC2-NA, CS04m12-SC2-NA, CS04m13-SC2-NA, CS04m23-SC2-NA, CS04m24-SC2-NA, CS04m34-SC2-NA, CS04m123-SC2-NA, CS04m234-SC2-NA, CS23m1-SC2-NA, CS23m2-SC2-NA, CS23m3-SC2-NA, CS23m4-SC2-NA, CS23m12-SC2-NA, CS23m13-SC2-NA, CS23m23-SC2-NA, CS23m24-SC2-NA, CS23m34-SC2-NA, CS23m123-SC2-NA, and CS23m234-SC2-NA.

[0071] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99.5% identity to a sequence selected from the group consisting of CS01-FL-NA, CS01-HC-NA, CS01-LC-NA, CS04-FL-NA, CS04-HC-NA, CS04-LC-NA, CS23-FL-NA, CS23-HC-NA, CS23-LC-NA, CS01m1-FL-NA, CS01m2-FL-NA, CS01m3-FL-NA, CS01m4-FL-NA, CS01m12-FL-NA, CS01m13-FL-NA, CS01m23-FL-NA, CS01m24-FL-NA, CS01m34-FL-NA, CS01m123-FL-NA, CS01m234-FL-NA, CS04m1-FL-NA, CS04m2-FL-NA, CS04m3-FL-NA, CS04m4-FL-NA, CS04m12-FL-NA, CS04m13-FL-NA, CS04m23-FL-NA, CS04m24-FL-NA, CS04m34-FL-NA, CS04m123-FL-NA, CS04m234-FL-NA, CS23m1-FL-NA, CS23m2-FL-NA, CS23m3-FL-NA, CS23m4-FL-NA, CS23m12-FL-NA, CS23m13-FL-NA, CS23m23-FL-NA, CS23m24-FL-NA, CS23m34-FL-NA, CS23m123-FL-NA, CS23m234-FL-NA, CS01-SC1-NA, CS04-SC1-NA, CS23-SC1-NA, CS01m1-SC1-NA, CS01m2-SC1-NA, CS01m3-SC1-NA, CS01m4-SC1-NA, CS01m12-SC1-NA, CS01m13-SC1-NA, CS01m23-SC1-NA, CS01m24-SC1-NA, CS01m34-SC1-NA, CS01m123-SC1-NA, CS01m234-SC1-NA, CS04m1-SC1-NA, CS04m2-SC1-NA, CS04m3-SC1-NA, CS04m4-SC1-NA, CS04m12-SC1-NA, CS04m13-SC1-NA, CS04m23-SC1-NA, CS04m24-SC1-NA, CS04m34-SC1-NA, CS04m123-SC1-NA, CS04m234-SC1-NA, CS23m1-SC1-NA, CS23m2-SC1-NA, CS23m3-SC1-NA, CS23m4-SC1-NA, CS23m12-SC1-NA, CS23m13-SC1-NA, CS23m23-SC1-NA, CS23m24-SC1-NA, CS23m34-SC1-NA, CS23m123-SC1-NA, CS23m234-SC1-NA, CS01-SC2-NA, CS04-SC2-NA, CS23-SC2-NA, CS01m1-SC2-NA, CS01m2-SC2-NA, CS01m3-SC2-NA, CS01m4-SC2-NA, CS01m12-SC2-NA, CS01m13-SC2-NA, CS01m23-SC2-NA, CS01m24-SC2-NA, CS01m34-SC2-NA, CS01m123-SC2-NA, CS01m234-SC2-NA, CS04m1-SC2-NA, CS04m2-SC2-NA, CS04m3-SC2-NA, CS04m4-SC2-NA, CS04m12-SC2-NA, CS04m13-SC2-NA, CS04m23-SC2-NA, CS04m24-SC2-NA, CS04m34-SC2-NA, CS04m123-SC2-NA, CS04m234-SC2-NA, CS23m1-SC2-NA, CS23m2-SC2-NA, CS23m3-SC2-NA, CS23m4-SC2-NA, CS23m12-SC2-NA, CS23m13-SC2-NA, CS23m23-SC2-NA, CS23m24-SC2-NA, CS23m34-SC2-NA, CS23m123-SC2-NA, and CS23m234-SC2-NA.

[0072] In one embodiment of the polynucleotides described above, the nucleotide sequence has at least 99.5% identity to a sequence selected from the group consisting of CS01-FL-NA, CS01-HC-NA, CS01-LC-NA, CS04-FL-NA, CS04-HC-NA, CS04-LC-NA, CS23-FL-NA, CS23-HC-NA, CS23-LC-NA, CS01m1-FL-NA, CS01m2-FL-NA, CS01m3-FL-NA, CS01m4-FL-NA, CS01m12-FL-NA, CS01m13-FL-NA, CS01m23-FL-NA, CS01m24-FL-NA, CS01m34-FL-NA, CS01m123-FL-NA, CS01m234-FL-NA, CS04m1-FL-NA, CS04m2-FL-NA, CS04m3-FL-NA, CS04m4-FL-NA, CS04m12-FL-NA, CS04m13-FL-NA, CS04m23-FL-NA, CS04m24-FL-NA, CS04m34-FL-NA, CS04m123-FL-NA, CS04m234-FL-NA, CS23m1-FL-NA, CS23m2-FL-NA, CS23m3-FL-NA, CS23m4-FL-NA, CS23m12-FL-NA, CS23m13-FL-NA, CS23m23-FL-NA, CS23m24-FL-NA, CS23m34-FL-NA, CS23m123-FL-NA, CS23m234-FL-NA, CS01-SC1-NA, CS04-SC1-NA, CS23-SC1-NA, CS01m1-SC1-NA, CS01m2-SC1-NA, CS01m3-SC1-NA, CS01m4-SC1-NA, CS01m12-SC1-NA, CS01m13-SC1-NA, CS01m23-SC1-NA, CS01m24-SC1-NA, CS01m34-SC1-NA, CS01m123-SC1-NA, CS01m234-SC1-NA, CS04m1-SC1-NA, CS04m2-SC1-NA, CS04m3-SC1-NA, CS04m4-SC1-NA, CS04m12-SC1-NA, CS04m13-SC1-NA, CS04m23-SC1-NA, CS04m24-SC1-NA, CS04m34-SC1-NA, CS04m123-SC1-NA, CS04m234-SC1-NA, CS23m1-SC1-NA, CS23m2-SC1-NA, CS23m3-SC1-NA, CS23m4-SC1-NA, CS23m12-SC1-NA, CS23m13-SC1-NA, CS23m23-SC1-NA, CS23m24-SC1-NA, CS23m34-SC1-NA, CS23m123-SC1-NA, CS23m234-SC1-NA, CS01-SC2-NA, CS04-SC2-NA, CS23-SC2-NA, CS01m1-SC2-NA, CS01m2-SC2-NA, CS01m3-SC2-NA, CS01m4-SC2-NA, CS01m12-SC2-NA, CS01m13-SC2-NA, CS01m23-SC2-NA, CS01m24-SC2-NA, CS01m34-SC2-NA, CS01m123-SC2-NA, CS01m234-SC2-NA, CS04m1-SC2-NA, CS04m2-SC2-NA, CS04m3-SC2-NA, CS04m4-SC2-NA, CS04m12-SC2-NA, CS04m13-SC2-NA, CS04m23-SC2-NA, CS04m24-SC2-NA, CS04m34-SC2-NA, CS04m123-SC2-NA, CS04m234-SC2-NA, CS23m1-SC2-NA, CS23m2-SC2-NA, CS23m3-SC2-NA, CS23m4-SC2-NA, CS23m12-SC2-NA, CS23m13-SC2-NA, CS23m23-SC2-NA, CS23m24-SC2-NA, CS23m34-SC2-NA, CS23m123-SC2-NA, and CS23m234-SC2-NA.

[0073] In one embodiment of the polynucleotides described above, the nucleotide sequence is selected from the group consisting of CS01-FL-NA, CS01-HC-NA, CS01-LC-NA, CS04-FL-NA, CS04-HC-NA, CS04-LC-NA, CS23-FL-NA, CS23-HC-NA, CS23-LC-NA, CS01m1-FL-NA, CS01m2-FL-NA, CS01m3-FL-NA, CS01m4-FL-NA, CS01m12-FL-NA, CS01m13-FL-NA, CS01m23-FL-NA, CS01m24-FL-NA, CS01m34-FL-NA, CS01m123-FL-NA, CS01m234-FL-NA, CS04m1-FL-NA, CS04m2-FL-NA, CS04m3-FL-NA, CS04m4-FL-NA, CS04m12-FL-NA, CS04m13-FL-NA, CS04m23-FL-NA, CS04m24-FL-NA, CS04m34-FL-NA, CS04m123-FL-NA, CS04m234-FL-NA, CS23m1-FL-NA, CS23m2-FL-NA, CS23m3-FL-NA, CS23m4-FL-NA, CS23m12-FL-NA, CS23m13-FL-NA, CS23m23-FL-NA, CS23m24-FL-NA, CS23m34-FL-NA, CS23m123-FL-NA, CS23m234-FL-NA, CS01-SC1-NA, CS04-SC1-NA, CS23-SC1-NA, CS01m1-SC1-NA, CS01m2-SC1-NA, CS01m3-SC1-NA, CS01m4-SC1-NA, CS01m12-SC1-NA, CS01m13-SC1-NA, CS01m23-SC1-NA, CS01m24-SC1-NA, CS01m34-SC1-NA, CS01m123-SC1-NA, CS01m234-SC1-NA, CS04m1-SC1-NA, CS04m2-SC1-NA, CS04m3-SC1-NA, CS04m4-SC1-NA,

CS04m12-SC1-NA, CS04m13-SC1-NA, CS04m23-SC1-NA, CS04m24-SC1-NA, CS04m34-SC1-NA, CS04m123-SC1-NA, CS04m234-SC1-NA, CS23m1-SC1-NA, CS23m2-SC1-NA, CS23m3-SC1-NA, CS23m4-SC1-NA, CS23m12-SC1-NA, CS23m13-SC1-NA, CS23m23-SC1-NA, CS23m24-SC1-NA, CS23m34-SC1-NA, CS23m123-SC1-NA, CS23m234-SC1-NA, CS01-SC2-NA, CS04-SC2-NA, CS23-SC2-NA, CS01m1-SC2-NA, CS01m2-SC2-NA, CS01m3-SC2-NA, CS01m4-SC2-NA, CS01m12-SC2-NA, CS01m13-SC2-NA, CS01m23-SC2-NA, CS01m24-SC2-NA, CS01m34-SC2-NA, CS01m123-SC2-NA, CS01m234-SC2-NA, CS04m1-SC2-NA, CS04m2-SC2-NA, CS04m3-SC2-NA, CS04m4-SC2-NA, CS04m12-SC2-NA, CS04m13-SC2-NA, CS04m23-SC2-NA, CS04m24-SC2-NA, CS04m34-SC2-NA, CS04m123-SC2-NA, CS04m234-SC2-NA, CS23m1-SC2-NA, CS23m2-SC2-NA, CS23m3-SC2-NA, CS23m4-SC2-NA, CS23m12-SC2-NA, CS23m13-SC2-NA, CS23m23-SC2-NA, CS23m24-SC2-NA, CS23m34-SC2-NA, CS23m123-SC2-NA, and CS23m234-SC2-NA.

[0074] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide comprises a glycosylation polypeptide positioned between two consecutive amino acids.

[0075] In one embodiment of the polynucleotides described above, the encoded polypeptide linker includes a glycosylation peptide with an amino acid sequence having at least 92% identity to a glycosylation peptide selected from the group consisting of NG1-AA, NG4-AA, NG5-AA, NG6-AA, NG7-AA, NG9-AA, NG10-AA, NG16-AA, NG17-AA, NG18-AA, NG19-AA, NG20-AA, NG21-AA and NGV-AA.

[0076] In one embodiment of the polynucleotides described above, the encoded polypeptide linker comprises a glycosylation peptide with an amino acid sequence selected from the group consisting of NG1-AA, NG4-AA, NG5-AA, NG6-AA, NG7-AA, NG9-AA, NG10-AA, NG16-AA, NG17-AA, NG18-AA, NG19-AA, NG20-AA, NG21-AA and NGV-AA.

[0077] In one embodiment of the polynucleotides described above, the glycosylation peptide is encoded by a polynucleotide with a nucleotide sequence having at least 95% identity to a sequence selected from the group consisting of NG1-NA, NG4-NA, NG5-NA, NG6-NA, NG7-NA, NG9-NA, NG10-NA, NG16-NA, NG17-NA, NG18-NA, NG19-NA, NG20-NA, NG21-NA and NGV-NA.

[0078] In one embodiment of the polynucleotides described above, the glycosylation peptide is encoded by a polynucleotide with a nucleotide sequence selected from one of NG1-NA, NG4-NA, NG5-NA, NG6-NA, NG7-NA, NG9-NA, NG10-NA, NG16-NA, NG17-NA, NG18-NA, NG19-NA, NG20-NA, NG21-NA and NGV-NA.

[0079] In one embodiment of the polynucleotides described above, the polypeptide linker is encoded by a third nucleotide sequence having at least 95% identity to a sequence selected from the group consisting of BDLNG1-NA, BDLNG3-NA, BDLNG5-NA, BDLNG6-NA, BDLNG9-NA, BDLNG10-NA, BDLNG16-NA, BDLNG17-NA, BDLNG18-NA, BDLNG19-NA, BDLNG20-NA and BDLNG21-NA.

[0080] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes an F328S (SPI, F309S SPE) amino acid substitution, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0081] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes I105V, A127S, G151K, M166T, and L171P (SPI; I86V, A108S, G132K, M147T, and L152P, SPE, respectively) amino acid substitutions, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0082] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes a) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), and b) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19). In some embodiments (e.g., where the encoded FVIII molecule includes a portion of the N-terminal region of the wild-type B-domain), the encoded Factor VIII polypeptide also includes a deletion of amino acids SF760-761, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0083] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes a) an F328S (SPI; F309S SPE) amino acid substitution, relative to FVIII-FL-AA (SEQ ID NO: 19), and b) C1918G and C1922G (SPI; C1899G and C1903 SPE, respectively) amino acid substitutions, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0084] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes a) an F328S (SPI; F309S SPE) amino acid substitution, relative to FVIII-FL-AA (SEQ ID NO: 19), and b) I105V, A127S, G151K, M166T, and L171P (SPI; I86V, A108S, G132K, M147T, and L152P, SPE, respectively) amino acid substitutions, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0085] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes a) an F328S amino acid substitution, relative to FVIII-FL-AA (SEQ ID NO: 19), b) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), and c) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19). In some embodiments (e.g., where the encoded FVIII molecule includes a portion of the N-terminal region of the wild-type B-domain), the encoded Factor VIII polypeptide also includes a deletion of amino acids SF760-761, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0086] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes a) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, relative to FVIII-FL-AA (SEQ ID NO: 19), b) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), and c) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19). In some embodiments (e.g., where the encoded FVIII molecule includes a portion of the N-terminal region of the wild-type B-domain), the encoded Factor VIII polypeptide also includes a deletion of amino acids SF760-761, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0087] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes a) an F328S amino acid substitution, relative to FVIII-FL-AA (SEQ ID NO: 19), b) C1918G and C1922G amino acid substitutions, relative to FVIII-FL-AA (SEQ ID

NO: 19), and c) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0088] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes a) an F328S amino acid substitution, relative to FVIII-FL-AA (SEQ ID NO: 19), b) C1918G and C1922G amino acid substitutions, relative to FVIII-FL-AA (SEQ ID NO: 19), c) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), and d) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19). In some embodiments (e.g., where the encoded FVIII molecule includes a portion of the N-terminal region of the wild-type B-domain), the encoded Factor VIII polypeptide also includes a deletion of amino acids SF760-761, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0089] In one embodiment of the polynucleotides described above, the encoded Factor VIII polypeptide includes a) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, relative to FVIII-FL-AA (SEQ ID NO: 19), b) an F328S amino acid substitution, relative to FVIII-FL-AA (SEQ ID NO: 19), c) C1918G and C1922G amino acid substitutions, relative to FVIII-FL-AA (SEQ ID NO: 19), d) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), and e) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19). In some embodiments (e.g., where the encoded FVIII molecule includes a portion of the N-terminal region of the wild-type B-domain), the encoded Factor VIII polypeptide also includes a deletion of amino acids SF760-761, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0090] In one embodiment of the polynucleotides described above, the polynucleotide also includes a promoter element operably linked to the polynucleotide encoding the Factor VIII polypeptide.

[0091] In one embodiment of the polynucleotides described above, the polynucleotide also includes an enhancer element operably linked to the polynucleotide encoding the Factor VIII polypeptide.

[0092] In one embodiment of the polynucleotides described above, the polynucleotide also includes a polyadenylation element operably linked to the polynucleotide encoding the Factor VIII polypeptide.

[0093] In one embodiment of the polynucleotides described above, the polynucleotide also includes an intron operatively linked to the nucleotide sequence encoding the Factor VIII polypeptide.

[0094] In one embodiment of the polynucleotides described above, the intron is positioned between a promoter element and the translation initiation site (e.g., the first coding ATG) of the nucleotide sequence encoding a Factor VIII polypeptide.

[0095] In another aspect, the disclosure provides a mammalian gene therapy vector including a polynucleotide as described above.

[0096] In one embodiment of the mammalian gene therapy vector described above, the mammalian gene therapy vector is an adeno-associated virus (AAV) vector.

[0097] In one embodiment of the mammalian gene therapy vector described above, the AAV vector is an AAV-8 vector.

[0098] In another aspect, the disclosure provides a method for treating hemophilia A including administering, to a patient in need thereof, a mammalian gene therapy vector as described above.

[0099] In another aspect, the disclosure provides a mammalian gene therapy vector as described above for treating hemophilia A.

[0100] In another aspect, the disclosure provides the use of a mammalian gene therapy vector as described above for the manufacture of a medicament for treating hemophilia A.

[0101] In another aspect, the disclosure provides a Factor VIII polypeptide including a light chain, a heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide has a sequence at least 95% identical to the sequence CS01-HC-AAm23. The light chain of the Factor VIII polypeptide has a sequence at least 95% identical to the sequence CS01-LC-AAm23. The polypeptide linker of the Factor VIII polypeptide includes a furin cleavage site. The Factor VIII polypeptide includes i) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, ii) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), and iii) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0102] In another aspect, the disclosure provides a Factor VIII polypeptide including a light chain, a heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide has a sequence at least 95% identical to the sequence CS01-HC-AAm123. The light chain of the Factor VIII polypeptide has a sequence at least 95% identical to the sequence CS01-LC-AAm123. The polypeptide linker of the Factor VIII polypeptide includes a furin cleavage site. The Factor VIII polypeptide includes i) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, ii) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), iii) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19), and iv) an F328S amino acid substitution.

[0103] In another aspect, the disclosure provides a Factor VIII polypeptide including a light chain, a heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide has a sequence at least 95% identical to the sequence CS01-HC-AAm234. The light chain of the Factor VIII polypeptide has a sequence at least 95% identical to the sequence CS01-LC-AAm234. The polypeptide linker of the Factor VIII polypeptide includes a furin cleavage site. The Factor VIII polypeptide includes i) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, ii) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), iii) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19), and iv) F328S/C1918G/C1922G amino acid substitutions.

[0104] In one embodiment of the Factor VIII polypeptides described, the heavy chain of the Factor VIII polypeptide has a sequence at least 96% identical to the respective heavy chain sequence (e.g., CS01-HC-AAm23, CS01-HC-AAm123, or CS01-HC-AAm234), and the light chain of the Factor FVIII polypeptide has a sequence at least 96%

identical to the respective light chain sequence (e.g., CS01-LC-AAm23, CS01-LC-AAm123, or CS01-LC-AAm234).

[0105] In one embodiment of the Factor VIII polypeptides described, the heavy chain of the Factor VIII polypeptide has a sequence at least 97% identical to the respective heavy chain sequence (e.g., CS01-HC-AAm23, CS01-HC-AAm123, or CS01-HC-AAm234), and the light chain of the Factor FVIII polypeptide has a sequence at least 97% identical to the respective light chain sequence (e.g., CS01-LC-AAm23, CS01-LC-AAm123, or CS01-LC-AAm234).

[0106] In one embodiment of the Factor VIII polypeptides described, the heavy chain of the Factor VIII polypeptide has a sequence at least 98% identical to the respective heavy chain sequence (e.g., CS01-HC-AAm23, CS01-HC-AAm123, or CS01-HC-AAm234), and the light chain of the Factor FVIII polypeptide has a sequence at least 98% identical to the respective light chain sequence (e.g., CS01-LC-AAm23, CS01-LC-AAm123, or CS01-LC-AAm234).

[0107] In one embodiment of the Factor VIII polypeptides described, the heavy chain of the Factor VIII polypeptide has a sequence at least 99% identical to the respective heavy chain sequence (e.g., CS01-HC-AAm23, CS01-HC-AAm123, or CS01-HC-AAm234), and the light chain of the Factor FVIII polypeptide has a sequence at least 99% identical to the respective light chain sequence (e.g., CS01-LC-AAm23, CS01-LC-AAm123, or CS01-LC-AAm234).

[0108] In one embodiment of the Factor VIII polypeptides described, the heavy chain of the Factor VIII polypeptide has a sequence at least 99.5% identical to the respective heavy chain sequence (e.g., CS01-HC-AAm23, CS01-HC-AAm123, or CS01-HC-AAm234), and the light chain of the Factor FVIII polypeptide has a sequence at least 99.5% identical to the respective light chain sequence (e.g., CS01-LC-AAm23, CS01-LC-AAm123, or CS01-LC-AAm234).

[0109] In one embodiment of the Factor VIII polypeptides described, the heavy chain of the Factor VIII polypeptide has a sequence identical to the respective heavy chain sequence (e.g., CS01-HC-AAm23, CS01-HC-AAm123, or CS01-HC-AAm234), and the light chain of the Factor FVIII polypeptide has a sequence identical to the respective light chain sequence (e.g., CS01-LC-AAm23, CS01-LC-AAm123, or CS01-LC-AAm234).

[0110] In one embodiment of the Factor VIII polypeptides described above, the polypeptide linker has at least 95% identity to BDL-SQ-AA (SEQ ID NO: 30).

[0111] In one embodiment of the Factor VIII polypeptides described above, the polypeptide linker has the amino acid sequence of BDL-SQ-AA (SEQ ID NO: 30).

[0112] In one embodiment of the Factor VIII polypeptides described above, the polypeptide linker includes a glycosylation peptide with an amino acid sequence having at least 92% identity to a glycosylation peptide selected from the group consisting of NG1-AA, NG4-AA, NG5-AA, NG6-AA, NG7-AA, NG9-AA, NG10-AA, NG16-AA, NG17-AA, NG18-AA, NG19-AA, NG20-AA, NG21-AA and NGV-AA.

[0113] In one embodiment of the Factor VIII polypeptides described above, the polypeptide linker includes a glycosylation peptide selected from the group consisting of NG1-AA, NG4-AA, NG5-AA, NG6-AA, NG7-AA, NG9-AA, NG10-AA, NG16-AA, NG17-AA, NG18-AA, NG19-AA, NG20-AA, NG21-AA and NGV-AA.

[0114] In one embodiment of the Factor VIII polypeptides described above, the polypeptide linker has an amino acid sequence having at least 95% identity to a sequence selected from the group consisting of BDLNG1-AA, BDLNG3-AA, BDLNG5-AA, BDLNG6-AA, BDLNG9-AA, BDLNG10-AA, BDLNG16-AA, BDLNG17-AA, BDLNG18-AA, BDLNG19-AA, BDLNG20-AA and BDLNG21-AA.

[0115] In one embodiment of the Factor VIII polypeptides described above, the polypeptide linker has an amino acid sequence selected from the group consisting of BDLNG1-AA, BDLNG3-AA, BDLNG5-AA, BDLNG6-AA, BDLNG9-AA, BDLNG10-NA, BDLNG16-AA, BDLNG17-AA, BDLNG18-AA, BDLNG19-AA, BDLNG20-AA and BDLNG21-AA.

[0116] In another aspect, the disclosure provides a Factor VIII polypeptide having an amino acid sequence with at least 95% identity to CS40-FL-AAm23 (SEQ ID NO: 104). The Factor VIII polypeptide includes i) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, ii) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), and iii) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19).

[0117] In another aspect, the disclosure provides a Factor VIII polypeptide having an amino acid sequence with at least 95% identity to CS40-FL-AAm123. The Factor VIII polypeptide includes i) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, ii) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), iii) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19), and iv) an F328S amino acid substitution.

[0118] In another aspect, the disclosure provides a Factor VIII polypeptide having an amino acid sequence with at least 95% identity to CS40-FL-AAm234. The Factor VIII polypeptide includes i) I105V, A127S, G151K, M166T, and L171P amino acid substitutions, ii) a deletion of amino acids AIEPR755-759, relative to FVIII-FL-AA (SEQ ID NO: 19), iii) an insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19), and iv) F328S/C1918G/C1922G amino acid substitutions.

[0119] In one embodiment of the Factor VIII polypeptides described, the Factor VIII polypeptide has a sequence at least 96% identical to the respective full-length sequence (e.g., CS40-FL-AAm23 (SEQ ID NO: 104), CS40-FL-AAm123, or CS40-FL-AAm234).

[0120] In one embodiment of the Factor VIII polypeptides described, the Factor VIII polypeptide has a sequence at least 97% identical to the respective full-length sequence (e.g., CS40-FL-AAm23 (SEQ ID NO: 104), CS40-FL-AAm123, or CS40-FL-AAm234).

[0121] In one embodiment of the Factor VIII polypeptides described, the Factor VIII polypeptide has a sequence at least 98% identical to the respective full-length sequence (e.g., CS40-FL-AAm23 (SEQ ID NO: 104), CS40-FL-AAm123, or CS40-FL-AAm234).

[0122] In one embodiment of the Factor VIII polypeptides described, the Factor VIII polypeptide has a sequence at least 99% identical to the respective full-length sequence (e.g., CS40-FL-AAm23 (SEQ ID NO: 104), CS40-FL-AAm123, or CS40-FL-AAm234).

[0123] In one embodiment of the Factor VIII polypeptides described, the Factor VIII polypeptide has a sequence at least 99.5% identical to the respective full-length sequence (e.g., CS40-FL-AAm23 (SEQ ID NO: 104), CS40-FL-AAm123, or CS40-FL-AAm234).

[0124] In one embodiment of the Factor VIII polypeptides described, the Factor VIII polypeptide has a sequence identical to the respective full-length sequence (e.g., CS40-FL-AAm23 (SEQ ID NO: 104), CS40-FL-AAm123, or CS40-FL-AAm234).

BRIEF DESCRIPTION OF DRAWINGS

[0125] FIG. **1** shows schematic illustrations of the wild-type and ReFacto-type human Factor VIII protein constructs.

[0126] FIGS. **2**A and **2**B show the CS04 codon-altered nucleotide sequence (SEQ ID NO: 1) encoding a Factor VIII variant in accordance with some embodiments ("CS04-FL-NA" for full-length coding sequence).

[0127] FIG. **3** shows the Factor VIII variant amino acid sequence (SEQ ID NO: 2) encoded by the CS04 codon-altered nucleotide sequence in accordance with some embodiments ("CS04-FL-AA" for full-length amino acid sequence).

[0128] FIG. **4** shows the portion of the CS04 codon-altered nucleotide sequence (SEQ ID NO: 3) encoding the heavy chain of a Factor VIII variant in accordance with some embodiments ("CS04-HC-NA").

[0129] FIG. **5** shows the portion of the CS04 codon-altered nucleotide sequence (SEQ ID NO: 4) encoding the light chain of a Factor VIII variant in accordance with some embodiments ("CS04-LC-NA").

[0130] FIG. **6** shows exemplary coding sequences (SEQ ID NOS 5-7 and 36-48, respectively, in order of appearance) for B-domain substituted linkers in accordance with some embodiments. BDLO01 (SEQ ID NO: 5), BDLO04 (SEQ ID NO: 6), and BDLO23 (SEQ ID NO: 7) are the respective portions of the CS01, CS04, and CS23 codon-altered nucleotide sequences that encode a B-domain substituted linker, respectively.

[0131] FIGS. **7**A, **7**B, and **7**C show an AAV vector sequence (SEQ ID NO: 8) containing an CS04 codon-altered nucleotide sequence in accordance with some embodiments ("CS04-AV-NA").

[0132] FIGS. **8**A and **8**B show the CS01m1 codon-altered nucleotide sequence (SEQ ID NO: 49) encoding a Factor VIII variant with an F328S amino acid substitution in accordance with some embodiments ("CS01m1-FL-NA").

[0133] FIGS. **9**A and **9**B show the CS04Δ(760-1667) (SPI; CS04Δ(741-1648), SPE) codon-altered nucleotide sequence (SEQ ID NO: 9) encoding a single-chain Factor VIII variant in accordance with some embodiments ("CS04-SC1-NA").

[0134] FIG. **10** shows the Factor VIII variant amino acid sequence (SEQ ID NO: 10) encoded by the CS01Δ(760-1667) (SPI; CS01Δ(741-1648), SPE), CS04Δ(760-1667) (SPI; CS04Δ(741-1648), SPE), and CS23Δ(760-1667) (SPI; CS23Δ(741-1648), SPE) codon-altered nucleotide sequences in accordance with some embodiments ("CS01-SC1-AA," "CS04-SC1-AA," and "CS23-SC1-AA," respectively).

[0135] FIGS. **11**A and **11**B show the CS04Δ(772-1667) (SPI; CS04Δ(753-1648), SPE) codon-altered nucleotide sequence (SEQ ID NO: 11) encoding a single-chain Factor VIII variant in accordance with some embodiments ("CS04-SC2-NA").

[0136] FIG. **12** shows the Factor VIII variant amino acid sequence (SEQ ID NO: 12) encoded by the CS01Δ(772-1667) (SPI; CS01Δ(753-1648), SPE), CS04Δ(772-1667) (SPI; CS04Δ(753-1648), SPE), and CS23Δ(772-1667) (SPI; CS23Δ(753-1648), SPE) codon-altered nucleotide sequence in accordance with some embodiments ("CS01-SC2-AA," "CS04-SC2-AA," and "CS23-SC2-AA," respectively).

[0137] FIGS. **13**A and **13**B show amino acid and nucleotide sequences for exemplary glycosylation peptides that are inserted into the B-domain substituted linker in accordance with some embodiments. "NG1" or NG1-AA" is the code for the amino acid sequence, shown in the top line. "NG1-NA" is the code for the nucleic acid sequence, shown in the bottom line for each set. FIGS. **13**A and **13**B disclose the amino acid sequences as SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, and the nucleotide sequences as SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, all respectively, in order of appearance.

[0138] FIG. **14** shows the results of in silico prediction of in vivo N-glycosylation of the wild-type Factor VIII B-domain. Figure discloses SEQ ID NOS 76 and 76-82, respectively, in order of appearance.

[0139] FIG. **15** shows the results of in silico prediction of in vivo N-glycosylation of the V3 peptide linker. Figure discloses SEQ ID NOS 83 and 83-89, respectively, in order of appearance.

[0140] FIGS. **16**A and **16**B show the CS01 codon-altered nucleotide sequence (SEQ ID NO: 13) encoding a Factor VIII variant in accordance with some embodiments ("CS01-FL-NA").

[0141] FIGS. **17**A and **17**B show the CS08 codon-altered nucleotide sequence (SEQ ID NO: 14) encoding a Factor VIII variant in accordance with some embodiments ("CS08-FL-NA").

[0142] FIGS. **18**A and **18**B show the CS10 codon-altered nucleotide sequence (SEQ ID NO: 15) encoding a Factor VIII variant in accordance with some embodiments ("CS10-FL-NA").

[0143] FIGS. **19**A and **19**B show the CS11 codon-altered nucleotide sequence (SEQ ID NO: 16) encoding a Factor VIII variant in accordance with some embodiments ("CS11-FL-NA").

[0144] FIGS. **20**A and **20**B show the CS40 wild-type ReFacto coding sequence (SEQ ID NO: 17), in accordance with some embodiments ("CS40-FL-NA").

[0145] FIGS. **21**A and **21**B show the CH25 codon-altered nucleotide sequence (SEQ ID NO: 18) encoding a Factor VIII variant in accordance with some embodiments ("CH25-FL-NA").

[0146] FIG. **22** shows a wild-type human Factor VIII amino acid sequence (SEQ ID NO: 19), in accordance with some embodiments ("FVIII-FL-AA").

[0147] FIG. **23** illustrates the scheme for cloning the pCS40, pCS01, pCS04, pCS08, pCS10, pCS11, and pCh25 constructs, by inserting synthetic Refacto-type BDD-FVIII DNA sequences into the vector backbone pCh-BB01 via AscI and NotI restriction sites.

[0148] FIG. **24** shows the integrity of AAV vector genome preparations, as analyzed by agarose gel electrophoresis. Lane 1, DNA marker; lane 2, vCS40; lane 3, vCS01; lane 4, vCS04. The AAV vectors have all the same-sized genomes, migrating at approximately 5 kb (arrow, right side). The scale on the left side indicates size of the DNA fragments in kilobases (kb).

[0149] FIG. **25** shows the protein analysis of AAV vector preparations by PAGE and silver staining. Lane 1, protein marker (M); lane 2, vCS40, lane 3, vCS01; and lane 4, vCS04. The constructs all have the same AAV8 capsids

consisting of VP1, VP2, and VP3 (arrows right side). The scale on the left side indicates size of the protein marker in kilodaltons (kDa).

[0150] FIGS. **26**A and **26**B show the CS23 codon-altered nucleotide sequence (SEQ ID NO: 20) encoding a Factor VIII variant in accordance with some embodiments ("CS23-FL-NA").

[0151] FIG. **27** shows the Factor VIII variant amino acid sequence (SEQ ID NO: 21) encoded by the CS23 codon-altered nucleotide sequence in accordance with some embodiments ("CS23-FL-AA").

[0152] FIG. **28** shows the portion of the CS23 codon-altered nucleotide sequence (SEQ ID NO: 22) encoding the heavy chain of a Factor VIII variant in accordance with some embodiments ("CS23-HC-NA").

[0153] FIG. **29** shows the portion of the CS23 codon-altered nucleotide sequence (SEQ ID NO: 23) encoding the light chain of a Factor VIII variant in accordance with some embodiments("CS23-LC-NA").

[0154] FIGS. **30**A and **30**B show the CS01m13 codon-altered nucleotide sequence (SEQ ID NO: 90) encoding a Factor VIII variant with m1 (F328S) and m3 amino acid substitutions in accordance with some embodiments ("CS01-FL-NA-m13").

[0155] FIGS. **31**A and **31**B show the CS01m23 codon-altered nucleotide sequence (SEQ ID NO: 91) encoding a Factor VIII variant with the m2 and m3 mutation sets in accordance with some embodiments ("CS01-FL-NA-m23").

[0156] FIGS. **32**A and **32**B show the CS01m3 codon-altered nucleotide sequence (SEQ ID NO: 92) encoding a Factor VIII variant with m3 amino acid substitutions in accordance with some embodiments ("CS01-FL-NA-m3").

[0157] FIGS. **33**A and **33**B show the CS01m2 codon-altered nucleotide sequence (SEQ ID NO: 93) encoding a Factor VIII variant with the m2 mutation set (I105V/A127S/G151K/M166T/L171P (SPI)) amino acid substitutions in accordance with some embodiments ("CS01-FL-NA-m2").

[0158] FIGS. **34**A and **34**B show the CS04m2 codon-altered nucleotide sequence (SEQ ID NO: 94) encoding a Factor VIII variant with the m2 mutants (I105V/A127S/G151K/M166T/L171P (SPI)) amino acid substitutions in accordance with some embodiments ("CS01-FL-NA-m2").

[0159] FIGS. **35**A and **35**B show the CS04m3 codon-altered nucleotide sequence (SEQ ID NO: 95) encoding a Factor VIII variant with m3 amino acid substitutions in accordance with some embodiments ("CS04-FL-NA-m3").

[0160] FIGS. **36**A and **36**B show the CS04m23 codon-altered nucleotide sequence (SEQ ID NO: 96) encoding a Factor VIII variant with the m2 mutant set (I105V/A127S/G151K/M166T/L171P (SPI)) and m3 amino acid substitutions in accordance with some embodiments ("CS04-FL-NA-m23").

[0161] FIGS. **37**A and **37**B show the CS04m1 codon-altered nucleotide sequence (SEQ ID NO: 97) encoding a Factor VIII variant with an m1 (F328S) amino acid substitution in accordance with some embodiments ("CS04-FL-NA-m1").

[0162] FIGS. **38**A and **38**B show the CS04m13 codon-altered nucleotide sequence (SEQ ID NO: 98) encoding a Factor VIII variant with m1 and m3 amino acid substitutions in accordance with some embodiments ("CS04-FL-NA-m13")

[0163] FIGS. **39**A and **39**B show the CS23m13 codon-altered nucleotide sequence (SEQ ID NO: 99) encoding a Factor VIII variant with m1 and m3 amino acid substitutions in accordance with some embodiments ("CS23m13-FL-NA")

[0164] FIGS. **40**A and **40**B show the CS23m3 codon-altered nucleotide sequence (SEQ ID NO: 100) encoding a Factor VIII variant with m3 amino acid substitutions in accordance with some embodiments ("CS23-FL-NA-m3")

[0165] FIGS. **41**A and **41**B show the CS23m2 codon-altered nucleotide sequence (SEQ ID NO: 101) encoding a Factor VIII variant with the m2 mutant set (I105V/A127S/G151K/M166T/L171P amino acid substitutions) in accordance with some embodiments ("CS23-FL-NA-m2").

[0166] FIGS. **42**A and **42**B show the CS23m1 codon-altered nucleotide sequence (SEQ ID NO: 102) encoding a Factor VIII variant with an m1 (F328S) amino acid substitution in accordance with some embodiments ("CS23-FL-NA-m1").

[0167] FIGS. **43**A and **43**B show the CS23m23 codon-altered nucleotide sequence (SEQ ID NO: 103) encoding a Factor VIII variant with the m2 mutant set (I105V/A127S/G151K/M166T/L171P) and m3 amino acid substitutions in accordance with some embodiments ("CS23-FL-NA-m23").

[0168] FIG. **44** depicts cloning of the pCS constructs, done by inserting synthetic Refacto-type BDD-FVIII carrying different mutations (see inserted table) into the vector backbone pCh-BB01 via AscI and NotI restriction sites.

[0169] FIG. **45** depicts the protein analysis of AAV vector preparations by PAGE and silver staining. Lane 1, protein marker (M); lane 2, vCS01, lane 3, vCS17; lane 4, vCS19; lane 5, vCS20; lane 6, vCS40; lane 7, vCS04; lane 8, vCS17; lane 9, vCS24 construct. The constructs have all the same AAV8 capsids consisting of VP1, VP2 and VP3 (arrows right side). The scale on the left side indicates size of the protein marker in kilo Daltons (kDa).

[0170] FIG. **46** depicts the integrity of AAV vector genome preparations analyzed by agarose gel electrophoresis. Lane 1, DNA marker (M); lane 2, vCS04, lane 3, vCS17; lane 4, vCS20; lane 5, vCS24; lane 6, vCS16; lane 7, vCS40 construct. Vector load is 1.5E10 vg per lane. The AAV vectors have the same-sized genomes, migrating at approximately 5 kb (arrow, right side). The scale on the left side indicates size of the DNA fragments in kilobases (kb).

[0171] FIG. **47** shows the portion of the CS01 codon-altered nucleotide sequence (SEQ ID NO: 24) encoding the heavy chain of a Factor VIII variant in accordance with some embodiments ("CS01-HC-NA").

[0172] FIG. **48** shows the portion of the CS01 codon-altered nucleotide sequence (SEQ ID NO: 25) encoding the light chain of a Factor VIII variant in accordance with some embodiments("CS01-LC-NA").

[0173] FIGS. **49**A and **49**B show the CS01Δ(760-1667) (SPI; CS01Δ(741-1648), SPE) codon-altered nucleotide sequence (SEQ ID NO: 26) encoding a single-chain Factor VIII variant in accordance with some embodiments ("CS01-SC1-NA").

[0174] FIGS. **50**A and **50**B show the CS01Δ(772-1667) (SPI; CS01Δ(753-1648), SPE) codon-altered nucleotide sequence (SEQ ID NO: 27) encoding a single-chain Factor VIII variant in accordance with some embodiments ("CS01-SC2-NA").

[0175] FIGS. **51**A and **51**B show the CS23Δ(760-1667) (SPI; CS23Δ(741-1648), SPE) codon-altered nucleotide

sequence (SEQ ID NO: 28) encoding a single-chain Factor VIII variant in accordance with some embodiments ("CS23-SC1-NA").

[0176] FIGS. **52**A and **52**B show the CS23Δ(772-1667) (SPI; CS23Δ(753-1648), SPE) codon-altered nucleotide sequence (SEQ ID NO: 29) encoding a single-chain Factor VIII variant in accordance with some embodiments ("CS23-SC2-NA").

[0177] FIG. **53** shows the Factor VIII variant amino acid sequence (SEQ ID NO: 104) encoded by the CS01m23 codon-altered nucleotide sequence in accordance with some embodiments ("CS01m23-FL-AA").

[0178] FIG. **54** shows the Factor VIII variant amino acid sequence (SEQ ID NO: 105) encoded by the CS04m3 codon-altered nucleotide sequence in accordance with some embodiments ("CS01m23-FL-AA").

[0179] FIG. **55** shows the Factor VIII variant amino acid sequence (SEQ ID NO: 106) encoded by the CS01m12 codon-altered nucleotide sequence in accordance with some embodiments ("CS01m12-FL-AA").

[0180] FIG. **56** shows the Factor VIII variant amino acid sequence (SEQ ID NO: 107) encoded by the CS04m12 codon-altered nucleotide sequence in accordance with some embodiments ("CS04m12-FL-AA").

[0181] FIGS. **57**A and **57**B show the CS01m12 codon-altered nucleotide sequence (SEQ ID NO: 108) encoding a Factor VIII variant with m1 (F328S) and m2 amino acid substitutions in accordance with some embodiments ("CS01-FL-NAm12").

[0182] FIGS. **58**A and **58**B show the CS04m12 codon-altered nucleotide sequence (SEQ ID NO: 109) encoding a Factor VIII variant with m1 (F328S) and m2 amino acid substitutions in accordance with some embodiments ("CS04-FL-NAm12").

DETAILED DESCRIPTION OF DISCLOSURE

I. Introduction

[0183] AAV-based gene therapy holds great promise for the treatment of hemophiliacs. For hemophilia B, first clinical data are encouraging in that FIX levels of about 10% can be maintained in at least some patients for more than 1 year. For hemophilia A however, achieving therapeutic expression levels of 5-10% with AAV vectors remains challenging for various reasons. First, the Factor VIII coding sequence is too large for conventional AAV-based vectors. Second, engineered B-domain deleted or truncated Factor VIII constructs suffer from poor expression in vivo, even when codon-optimized. Third, these B-domain deleted or truncated Factor VIII variant constructs have short half-lives in vivo, exacerbating the effects of poor expression. Fourth, even when expressed, FVIII is not efficiently secreted from cells, as are other coagulation factors, such as Factor IX.

[0184] Moreover, these challenges cannot be addressed by simply administering higher doses of the gene therapy construct. According to current knowledge, the vector dose of an AAV-based gene therapy vector should be increased above 2×10^{12} vg/kg bodyweight. This is because at such high doses a T cell immune response is triggered, which destroys transduced cells and, as a consequence, transgene expression is reduced or even eliminated. Therefore, strategies to improve the expression of FVIII are needed to make FVIII gene therapy a viable therapeutic option for hemophilia A patients.

[0185] The present disclosure relates to the discovery of codon-altered Factor VIII variant coding sequences that solve these and other problems associated with Factor VIII gene therapy. For example, the polynucleotides disclosed herein provide markedly improved expression in mammalian cells, and display improved virion packaging due to stabilized packing interactions. In some implementations, these advantages are realized by using coding sequences for the heavy and light chains of Factor VIII with high sequence identity to the codon altered CS01, CS04, and CS23 constructs (e.g., with high sequence identity to one of the CS01-HC, CS04-HC, and CS23-HC heavy chain coding sequences and high sequence identity to one of the CS01-LC, CS04-LC, and CS23-LC light chain coding sequences).

[0186] In some implementations, the Factor VIII molecules encoded by the polynucleotides described herein have been shortened by truncating, deleting, or replacing the wild-type B-domain. As such, the polynucleotides are better suited for expressing Factor VIII via conventional gene therapy vectors, which inefficiently express larger polypeptides, such as the wild-type Factor VIII.

[0187] Advantageously, it is shown herein that the CS01, CS04, and CS23 codon-altered Factor VIII variant coding sequences provide superior expression of a B-domain deleted Factor VIII construct in vivo. For example, it is demonstrated in Example 2 and Example 4 that intravenous administration of AAV-based gene therapy vectors having the CS01 (SEQ ID NO: 13), CS04 (SEQ ID NO: 1), and CS23 (SEQ ID NO: 20) coding sequence provide 18-fold, 74-fold, and 30-fold increases in Factor VIII expression, relative to the corresponding CS40 construct encoded with the wild-type polynucleotide sequence (SEQ ID NO: 17), in Factor VIII knock-out mice (Table 4 and Table 7).

[0188] Further, it also shown herein that the CS01 and CS04 codon-altered Factor VIII variant coding sequences provide superior virion packaging and virus production. For example, it is demonstrated in Example 1 that AAV vector constructs containing the CS01 and CS04 constructs provided 5 to 7-fold greater viral yield, relative to the corresponding CS40 construct encoded with the wild-type polynucleotide sequence, when isolated from the same amount of cell pellet.

[0189] Advantageously, Applicants also found that the improved Factor VIII activity generated from the CS01, CS04, and CS23 codon altered sequences could be further enhanced by introducing mutations into the underlying Factor VIII polypeptide sequence. For example, as demonstrated in Example 4, the F328S, X5, and X1 mutations, alone and in combination with one another, further increased FVIII activity when expressed in vivo in the CS01 or CS04 codon altered background 2 to 7-fold, relative to the wild type, codon altered constructs (Table 7). More strikingly, these codon altered sequences, encoding the mutant Factor VIII mutants, provided up to 246-fold greater increase as compared to the corresponding CS40 construct encoded with the wild-type polynucleotide sequence (Table 7).

II. Definitions

[0190] As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0191] As used herein, the terms "Factor VIII" and "FVIII" are used interchangeably, and refer to any protein with Factor VIII activity (e.g., active FVIII, often referred to as FVIIIa) or protein precursor (e.g., pro-protein or pre-pro-

protein) of a protein with Factor VIII activity, particularly Factor IXa cofactor activity. In an exemplary embodiment, a Factor VIII polypeptide refers to a polypeptide that has sequences with high sequence identity (e.g., at least 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more) to the heavy and light chains of a wild type Factor VIII polypeptide. In some embodiments, the B-domain of a Factor VIII polypeptide is deleted, truncated, or replaced with a linker polypeptide to reduce the size of the polynucleotide encoding the Factor VIII polypeptide. In an exemplary embodiment, amino acids 20-1457 of SEQ ID NO: 2 constitute a Factor VIII polypeptide.

[0192] Non-limiting examples of wild type Factor VIII polypeptides include human pre-pro-Factor VIII (e.g., GenBank accession nos. AAA52485, CAA25619, AAA58466, AAA52484, AAA52420, AAV85964, BAF82636, BAG36452, CAI41660, CAI41666, CAI41672, CAI43241, CA003404, EAW72645, AAH22513, AAH64380, AAH98389, AAI11968, AAI11970, or AAB61261), corresponding pro-Factor VIII, and natural variants thereof; porcine pre-pro-Factor VIII (e.g., UniProt accession nos. F1RZ36 or K7GSZ5), corresponding pro-Factor VIII, and natural variants thereof; mouse pre-pro-Factor VIII (e.g., GenBank accession nos. AAA37385, CAM15581, CAM26492, or EDL29229), corresponding pro-Factor VIII, and natural variants thereof; rat pre-pro-Factor VIII (e.g., GenBank accession no. AAQ21580), corresponding pro-Factor VIII, and natural variants thereof; rat pre-pro-Factor VIII; and other mammalian Factor VIII homologues (e.g., monkey, ape, hamster, guinea pig, etc.).

[0193] As used herein, a Factor VIII polypeptide includes natural variants and artificial constructs with Factor IX cofactor activity. As used in the present disclosure, Factor VIII encompasses any natural variants, alternative sequences, isoforms, or mutant proteins that retain some basal Factor IX cofactor activity (e.g., at least 5%, 10%, 25%, 50%, 75%, or more of the corresponding wild type activity). Examples of Factor VIII amino acid variations (relative to FVIII-FL-AA (SEQ ID NO: 19)) found in the human population include, without limitation, S19R, R22T, Y24C, Y25C, L26P/R, E30V, W33G, Y35C/H, G41C, R48C/K, K67E/N, L69P, E72K, D75E/V/Y, P83R, G89D/V, G92A/V, A97P, E98K, V99D, D101G/H/V, V104D, K108T, M110V, A111T/V, H113R/Y, L117F/R, G121S, E129V, G130R, E132D, Y133C, D135G/Y, T137A/I, S138R, E141K, D145H, V147D, Y155H, V159A, N163K, G164D/V, P165S, C172W, S176P, S179P, V181E/M, K185T, D186G/N/Y, S189L, L191F, G193R, L195P, C198G, S202N/R, F214V, L217H, A219D/T, V220G, D222V, E223K, G224W, T252I, V253F, N254I, G255V, L261P, P262L, G263S, G266F, C267Y, W274C, H275L, G278R, G280D, E284K, V285G, E291G/K, T294I, F295L, V297A, N299I, R301C/H/L, A303E/P, I307S, S308L, F312S, T314A/I, A315V, G323E, L326P, L327P/V, C329F, I331V, M339T, E340K, V345A/L, C348R/S/Y, Y365C, R391C/H/P, S392L/P, A394S, W401G, I405F/S, E409G, W412G/R, K427I, L431F/S, R437P/W, I438F, G439D/S/V, Y442C, K444R, Y450D/N, T454I, F455C, G466E, P470L/R/T, G474E/R/V, E475K, G477V, D478N, T479R, F484C, A488G, R490G, Y492C/H, Y492H, I494T, P496R, G498R, R503H, G513S/V, I522Y, K529E, W532G, P540T, T541S, D544N, R546W, R550C/G/H, S553P, S554C/G, V556D, R560T, D561G/H/Y, I567T, P569R, S577F, V578A, D579A/H, N583S, Q584H/K/R, I585R/T, M586V, D588G/Y, L594Q, S596P, N601D/K, R602G, S603I/R, W604C, Y605H/S, N6091, R612C, N631K/S, M633I, S635N, N637D/I/S, Y639C, L644V, L650F, V653A/M, L659P, A663V, Q664P, F677L, M681I, V682F, Y683C/N, T686R, F698L, M699T/V, M701I, G705V, G710W, N713I, R717L/W, G720D/S, M721I/L, A723T, L725Q, V727F, E739K, Y742C, R795G, P947R, V1012L, E1057K, H1066Y, D1260E, K1289Q, Q1336K, N1460K, L1481P, A1610S, I1698T, Y1699C/F, E1701K, Q1705H, R1708C/H, T1714S, R1715G, A1720V, E1723K, D1727V, Y1728C, R1740G, K1751Q, F1762L, R1768H, G1769R, L1771P, L1775F/V, L1777P, G1779E/R, P1780L, I1782R, D1788H, M1791T, A1798P, S1799H, R1800C/G/H, P1801A, Y1802C, S1803Y, F1804S, L1808F, M1842I, P1844S, T1845P, E1848G, A1853T/V, S1858C, K1864E, D1865N/Y, H1867P/R, G1869D/V, G1872E, P1873R, L1875P, V1876L, C1877R/Y, L1882P, R1888I, E1894G, 11901F, E1904D/K, S1907C/R, W1908L, Y1909C, A1939T/V, N1941D/S, G1942A, M1945V, L1951F, R1960L/Q, L1963P, S1965I, M19661/V, G1967D, S1968R, N1971T, H1973L, G1979V, H1980P/Y, F1982I, R1985Q, L1994P, Y1998C, G2000A, T2004R, M2007I, G2013R, W2015C, R2016P/W, E2018G, G2022D, G2028R, S2030N, V2035A, Y2036C, N2038S, 2040Y, G2045E/V, 12051S, I2056N, A2058P, W2065R, P2067L, A2070V, S2082N, S2088F, D2093G/Y, H2101D, T2105N, Q2106E/P/R, G2107S, R2109C, I2117F/S, Q2119R, F2120C/L, Y2124C, R2135P, S2138Y, T2141N, M2143V, F2145C, N2148S, N2157D, P2162L, R2169C/H, P2172L/Q/R, T2173A/I, H2174D, R2178C/H/L, R2182C/H/P, M2183R/V, L2185S/W, S2192I, C2193G, P2196R, G2198V, E2200D, 12204T, 12209N, A2211P, A2220P, P2224L, R2228G/L/P/Q, L2229F, V2242M, W2248C/S, V2251A/E, M2257V, T2264A, Q2265R, F2279C/I, I2281T, D2286G, W2290L, G2304V, D2307A, P2319L/S, R2323C/G/H/L, R2326G/L/P/Q, Q2330P, W2332R, I2336F, R2339T, G2344C/D/S, and C2345S/Y. Factor VIII proteins also include polypeptides containing post-translational modifications.

[0194] Generally, polynucleotides encoding Factor VIII encode for an inactive single-chain polypeptide (e.g., a pre-pro-protein) that undergoes post-translational processing to form an active Factor VIII protein (e.g., FVIIIa). For example, referring to FIG. **1**, the wild type human Factor VIII pre-pro-protein is first cleaved to release the encoded signal peptide (not shown), forming a first single-chain pro-protein (shown as "human wild-type FVIII). The pro-protein is then cleaved between the B and A3 domains to form a first polypeptide that includes the Factor VIII heavy chain (e.g., the A1 and A2 domains) and B-domain, and a second polypeptide that includes the Factor VIII light chain (e.g., including the A3, C1, and C3 domains). The first polypeptide is further cleaved to remove the B-domain, and also to separate the A1 and A2 domains, which remain associated with the Factor VIII light chain in the mature Factor VIIIa protein. For review of the Factor VIII maturation process, see Graw et al., Nat Rev Genet., 6(6):488-501 (2005), the content of which is incorporated herein by reference in its entirety for all purposes.

[0195] However, in some embodiments, the Factor VIII polypeptide is a single-chain Factor VIII polypeptide. Single-chain Factor VIII polypeptides are engineered to remove natural cleavage sites, and optionally remove, truncate, or replace the B-domain of Factor VIII. As such, they are not matured by cleavage (other than cleavage of an

optional signal and/or leader peptide), and are active as a single chain. Non-limiting examples of single-chain Factor VIII polypeptides are described in Zollner et al. (Thromb Res, 134(1):125-31 (2014)) and Donath et al. (Biochem J., 312(1):49-55 (1995)), the disclosures of which are hereby incorporated by reference in their entireties for all purposes.

[0196] As used herein, the terms "Factor VIII heavy chain," or simply "heavy chain," refers to the aggregate of the A1 and A2 domains of a Factor VIII polypeptide. In an exemplary embodiment, amino acids 20-759 of CS04-FL-AA (SEQ ID NO: 2) constitute a Factor VIII heavy chain.

[0197] As used herein, the term "Factor VIII light chain," or simply "light chain," refers to the aggregate of the A3, C1, and C2 domains of a Factor VIII polypeptide. In an exemplary embodiment, amino acids 774-1457 CS04-FL-AA (SEQ ID NO: 2) constitute a Factor VIII light chain. In some embodiments, a Factor VIII light chain excludes the acidic a3 peptide, which is released during maturation in vivo.

[0198] Generally, Factor VIII heavy and light chains are expressed as a single polypeptide chain, e.g., along with an optional B-domain or B-domain substituted linker. However, in some embodiments, a Factor VIII heavy chain and Factor VIII light chain are expressed as separate polypeptide chains (e.g., co-expressed), and reconstituted to form a Factor VIII protein (e.g., in vivo or in vitro).

[0199] As used herein, the terms "B-domain substituted linker" and "Factor VIII linker" are used interchangeably, and refer to truncated versions of a wild type Factor VIII B-domain (e.g., amino acids 760-1667 of FVIII-FL-AA (SEQ ID NO: 19)) or peptides engineered to replace the B-domain of a Factor VIII polypeptide. As used herein, a Factor VIII linker is positioned between the C-terminus of a Factor VIII heavy chain and the N-terminus of a Factor VIII light chain in a Factor VIII variant polypeptide in accordance with some embodiments. Non-limiting examples of B-domain substituted linkers are disclosed in U.S. Pat. Nos. 4,868,112, 5,112,950, 5,171,844, 5,543,502, 5,595,886, 5,610,278, 5,789,203, 5,972,885, 6,048,720, 6,060,447, 6,114,148, 6,228,620, 6,316,226, 6,346,513, 6,458,563, 6,924,365, 7,041,635, and 7,943,374; U.S. Patent Application Publication Nos. 2013/024960, 2015/0071883, and 2015/0158930; and PCT Publication Nos. WO 2014/064277 and WO 2014/127215, the disclosures of which are hereby incorporated by reference, in their entireties, for all purposes.

[0200] Unless otherwise specified herein, the numbering of Factor VIII amino acids refers to the corresponding amino acid in the full-length, wild-type human Factor VIII sequence (FVIII-FL-AA), presented as SEQ ID NO: 19 in FIG. **22**. As such, when referring to an amino acid substitution in a Factor VIII variant protein disclosed herein, the recited amino acid number refers to the analogous (e.g., structurally or functionally equivalent) and/or homologous (e.g., evolutionarily conserved in the primary amino acid sequence) amino acid in the full-length, wild-type Factor VIII sequence. For example, a T2105N amino acid substitution refers to a T to N substitution at position 2105 of the full-length, wild-type human Factor VIII sequence (FVIII-FL-AA; SEQ ID NO: 19), a T to N substitution at position 1211 of the Factor VIII variant protein encoded by CS04 (CS04-FL-AA; SEQ ID NO: 2), and a T to N substitution at position 1212 of the Factor VIII variant encoded by CS04m3 (CS04m3-FL-AA; SEQ ID NO: 105).

[0201] As described herein, the Factor VIII amino acid numbering system is dependent on whether the Factor VIII signal peptide (e.g., amino acids 1-19 of the full-length, wild-type human Factor VIII sequence) is included. Where the signal peptide is included, the numbering is referred to as "signal peptide inclusive" or "SPI". Where the signal peptide is not included, the numbering is referred to as "signal peptide exclusive" or "SPE." For example, F328S is SPI numbering for the same amino acid as F309S, in SPE numbering. Unless otherwise indicated, all amino acid numbering refers to the corresponding amino acid in the full-length, wild-type human Factor VIII sequence (FVIII-FL-AA), presented as SEQ ID NO: 19 in FIG. **22**.

[0202] As described herein, the codon-altered polynucleotides provide increased expression of transgenic Factor VIII in vivo (e.g., when administered as part of a gene therapy vector), as compared to the level of Factor VIII expression provided by a natively-coded Factor VIII construct (e.g., a polynucleotide encoding the same Factor VIII construct using the wild-type human codons). As used herein, the term "increased expression" refers to an increased level of transgenic Factor VIII activity in the blood of an animal administered the codon-altered polynucleotide encoding Factor VIII, as compared to the level of transgenic Factor VIII activity in the blood of an animal administered a natively-coded Factor VIII construct. The activity levels can be measured using any Factor VIII activity known in the art. An exemplary assay for determining Factor VIII activity is the Technochrome FVIII assay (Technoclone, Vienna, Austria).

[0203] In some embodiments, increased expression refers to at least 25% greater transgenic Factor VIII activity in the blood of an animal administered the codon-altered Factor VIII polynucleotide, as compared to the level of transgenic Factor VIII activity in the blood of an animal administered a natively coded Factor VIII polynucleotide. In some embodiments, increased expression refers to at least 50% greater, at least 75% greater, at least 100% greater, at least 3-fold greater, at least 4-fold greater, at least 5-fold greater, at least 6-fold greater, at least 7-fold greater, at least 8-fold greater, at least 9-fold greater, at least 10-fold greater, at least 15-fold greater, at least 20-fold greater, at least 25-fold greater, at least 30-fold greater, at least 40-fold greater, at least 50-fold greater, at least 60-fold greater, at least 70-fold greater, at least 80-fold greater, at least 90-fold greater, at least 100-fold greater, at least 125-fold greater, at least 150-fold greater, at least 175-fold greater, at least 200-fold greater, at least 225-fold greater, or at least 250-fold greater transgenic Factor VIII activity in the blood of an animal administered the codon-altered Factor VIII polynucleotide, as compared to the level of transgenic Factor VIII activity in the blood of an animal administered a natively coded Factor VIII polynucleotide.

[0204] As described herein, the codon-altered polynucleotides provide increased vector production, as compared to the level of vector production provided by a natively-coded Factor VIII construct (e.g., a polynucleotide encoding the same Factor VIII construct using the wild-type human codons). As used herein, the term "increased virus production" refers to an increased vector yield in cell culture (e.g., titer per liter culture) inoculated with the codon-altered polynucleotide encoding Factor VIII, as compared to the vector yield in cell culture inoculated with a natively-coded Factor VIII construct. The vector yields can be measured

using any vector titer assay known in the art. An exemplary assay for determining vector yield (e.g., of an AAV vector) is qPCR targeting the AAV2 inverted terminal repeats (Aurnhammer, Human Gene Therapy Methods: Part B 23:18-28 (2012)).

[0205] In some embodiments, increased virus production refers to at least 25% greater codon-altered vector yield, as compared to the yield of a natively-coded Factor VIII construct in the same type of culture. In some embodiments, increased vector production refers to at least 50% greater, at least 75% greater, at least 100% greater, at least 3-fold greater, at least 4-fold greater, at least 5-fold greater, at least 6-fold greater, at least 7-fold greater, at least 8-fold greater, at least 9-fold greater, at least 10-fold greater, at least 15-fold greater, or at least 20-fold greater codon-altered vector yield, as compared to the yield of a natively-coded Factor VIII construct in the same type of culture.

[0206] As used herein, the term "hemophilia" refers to a group of disease states broadly characterized by reduced blood clotting or coagulation. Hemophilia may refer to Type A, Type B, or Type C hemophilia, or to the composite of all three diseases types. Type A hemophilia (hemophilia A) is caused by a reduction or loss of factor VIII (FVIII) activity and is the most prominent of the hemophilia subtypes. Type B hemophilia (hemophilia B) results from the loss or reduction of factor IX (FIX) clotting function. Type C hemophilia (hemophilia C) is a consequence of the loss or reduction in factor XI (FXI) clotting activity. Hemophilia A and B are X-linked diseases, while hemophilia C is autosomal. Conventional treatments for hemophilia include both prophylactic and on-demand administration of clotting factors, such as FVIII, FIX, including Bebulin®-VH, and FXI, as well as FEIBA-VH, desmopressin, and plasma infusions.

[0207] As used herein, the term "FVIII gene therapy" includes any therapeutic approach of providing a nucleic acid encoding Factor VIII to a patient to relieve, diminish, or prevent the reoccurrence of one or more symptoms (e.g., clinical factors) associated with hemophilia. The term encompasses administering any compound, drug, procedure, or regimen comprising a nucleic acid encoding a Factor VIII molecule, including any modified form of Factor VIII (e.g., Factor VIII variant), for maintaining or improving the health of an individual with hemophilia. One skilled in the art will appreciate that either the course of FVIII therapy or the dose of a FVIII therapeutic agent can be changed, e.g., based upon the results obtained in accordance with the present disclosure.

[0208] As used herein, the term "bypass therapy" includes any therapeutic approach of providing non-Factor VIII hemostatic agents, compounds or coagulation factors to a patient to relieve, diminish, or prevent the reoccurrence of one or more symptoms (e.g., clinical factors) associated with hemophilia. Non-Factor VIII compounds and coagulation factors include, but are not limited to, Factor VIII Inhibitor Bypass Activity (FEIBA), recombinant activated factor VII (FVIIa), prothrombin complex concentrates, and activated prothrombin complex concentrates. These non-Factor VIII compounds and coagulation factors may be recombinant or plasma-derived. One skilled in the art will appreciate that either the course of bypass therapy or the dose of bypass therapy can be changed, e.g., based upon the results obtained in accordance with the present disclosure.

[0209] As used herein, a "combination therapy" including administration of a nucleic acid encoding a Factor VIII molecule and a conventional hemophilia A therapeutic agent includes any therapeutic approach of providing both a nucleic acid encoding a Factor VIII molecule and a Factor VIII molecule and/or non-Factor VIII hemostatic agent (e.g., bypass therapeutic agent) to a patient to relieve, diminish, or prevent the reoccurrence of one or more symptoms (e.g., clinical factors) associated with hemophilia. The term encompasses administering any compound, drug, procedure, or regimen including a nucleic acid encoding a Factor VIII molecule, including any modified form of factor VIII, which is useful for maintaining or improving the health of an individual with hemophilia and includes any of the therapeutic agents described herein.

[0210] The terms "therapeutically effective amount or dose" or "therapeutically sufficient amount or dose" or "effective or sufficient amount or dose" refer to a dose that produces therapeutic effects for which it is administered. For example, a therapeutically effective amount of a drug useful for treating hemophilia can be the amount that is capable of preventing or relieving one or more symptoms associated with hemophilia. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy,* 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0211] As used herein, the term "gene" refers to the segment of a DNA molecule that codes for a polypeptide chain (e.g., the coding region). In some embodiments, a gene is positioned by regions immediately preceding, following, and/or intervening the coding region that are involved in producing the polypeptide chain (e.g., regulatory elements such as a promoter, enhancer, polyadenylation sequence, 5'-untranslated region, 3'-untranslated region, or intron).

[0212] As used herein, the term "regulatory elements" refers to nucleotide sequences, such as promoters, enhancers, terminators, polyadenylation sequences, introns, etc, that provide for the expression of a coding sequence in a cell.

[0213] As used herein, the term "promoter element" refers to a nucleotide sequence that assists with controlling expression of a coding sequence. Generally, promoter elements are located 5' of the translation start site of a gene. However, in certain embodiments, a promoter element may be located within an intron sequence, or 3' of the coding sequence. In some embodiments, a promoter useful for a gene therapy vector is derived from the native gene of the target protein (e.g., a Factor VIII promoter). In some embodiments, a promoter useful for a gene therapy vector is specific for expression in a particular cell or tissue of the target organism (e.g., a liver-specific promoter). In yet other embodiments, one of a plurality of well characterized promoter elements is used in a gene therapy vector described herein. Non-limiting examples of well-characterized promoter elements include the CMV early promoter, the β-actin promoter, and the methyl CpG binding protein 2 (MeCP2) promoter. In some embodiments, the promoter is a constitutive promoter, which drives substantially constant expression of the target protein. In other embodiments, the promoter is an inducible promoter, which drives expression of the target protein in response to a particular stimulus (e.g., exposure to a particular treatment or agent). For a review of designing promoters for AAV-mediated gene therapy, see Gray et al.

(Human Gene Therapy 22:1143-53 (2011)), the contents of which are expressly incorporated by reference in their entirety for all purposes.

[0214] As used herein, the term "vector" refers to any vehicle used to transfer a nucleic acid (e.g., encoding a Factor VIII gene therapy construct) into a host cell. In some embodiments, a vector includes a replicon, which functions to replicate the vehicle, along with the target nucleic acid. Non-limiting examples of vectors useful for gene therapy include plasmids, phages, cosmids, artificial chromosomes, and viruses, which function as autonomous units of replication in vivo. In some embodiments, a vector is a viral vehicle for introducing a target nucleic acid (e.g., a codon-altered polynucleotide encoding a Factor VIII variant). Many modified eukaryotic viruses useful for gene therapy are known in the art. For example, adeno-associated viruses (AAVs) are particularly well suited for use in human gene therapy because humans are a natural host for the virus, the native viruses are not known to contribute to any diseases, and the viruses illicit a mild immune response.

[0215] As used herein, the term "CpG island" refers to a region within a polynucleotide having a statistically elevated density of CpG dinucleotides. As used herein, a region of a polynucleotide (e.g., a polynucleotide encoding a codon-altered Factor VIII protein) is a CpG island if, over a 200-base pair window: (i) the region has GC content of greater than 50%, and (ii) the ratio of observed CpG dinucleotides per expected CpG dinucleotides is at least 0.6, as defined by the relationship:

$$\frac{N[CpG] * N[\text{length of window}]}{N[C] * N[G]} \geq 0.6.$$

For additional information on methods for identifying CpG islands, see Gardiner-Garden M. et al., J Mol Biol., 196(2): 261-82 (1987), the content of which is expressly incorporated herein by reference, in its entirety, for all purposes.

[0216] As used herein, the term "nucleic acid" refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form, and complements thereof. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, and peptide-nucleic acids (PNAs).

[0217] The term "amino acid" refers to naturally occurring and non-natural amino acids, including amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids include those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, y-carboxyglutamate, and O-phosphoserine. Naturally occurring amino acids can include, e.g., D- and L-amino acids. The amino acids used herein can also include non-natural amino acids. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., any carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, or methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refer to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that function in a manner similar to a naturally occurring amino acid. Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0218] The nucleotide sequences that encode the mutant Factor VIII constructs herein may be identical to the coding sequence provided herein or may be a different coding sequence, which sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same polypeptides as the coding sequences provided herein. One of ordinary skill in the art will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each variation of a nucleic acid which encodes a same polypeptide is implicit in each described sequence with respect to the expression product, but not with respect to actual gene therapy constructs.

[0219] As to amino acid sequences, one of ordinary skill in the art will recognize that individual substitutions, deletions or additions to a nucleic acid or peptide sequence that alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the disclosure.

[0220] Conservative amino acid substitutions providing functionally similar amino acids are well known in the art. Dependent on the functionality of the particular amino acid, e.g., catalytic, structural, or sterically important amino acids, different groupings of amino acid may be considered conservative substitutions for each other. Table 1 provides groupings of amino acids that are considered conservative substitutions based on the charge and polarity of the amino acid, the hydrophobicity of the amino acid, the surface exposure/structural nature of the amino acid, and the secondary structure propensity of the amino acid.

TABLE 1

Groupings of conservative amino acid substitutions based on the functionality of the residue in the protein.

Important Feature	Conservative Groupings
Charge/Polarity	1. H, R, and K 2. D and E 3. C, T, S, G, N, Q, and Y 4. A, P, M, L, I, V, F, and W

TABLE 1-continued

Groupings of conservative amino acid substitutions based on the functionality of the residue in the protein.

Important Feature	Conservative Groupings
Hydrophobicity	1. D, E, N, Q, R, and K 2. C, S, T, P, G, H, and Y 3. A, M, I, L, V, F, and W
Structural/Surface Exposure	1. D, E, N, Q, H, R, and K 2. C, S, T, P, A, G, W, and Y 3. M, I, L, V, and F
Secondary Structure Propensity	1. A, E, Q, H, K, M, L, and R 2. C, T, I, V, F, Y, and W 3. S, G, P, D, and N
Evolutionary Conservation	1. D and E 2. H, K, and R 3. N and Q 4. S and T 5. L, I, and V 6. F, Y, and W 7. A and G 8. M and C

[0221] The terms "identical" or percent "identity," in the context of two or more nucleic acids or peptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection.

[0222] As is known in the art, a number of different programs may be used to identify whether a protein (or nucleic acid as discussed below) has sequence identity or similarity to a known sequence. Sequence identity and/or similarity is determined using standard techniques known in the art, including, but not limited to, the local sequence identity algorithm of Smith & Waterman, Adv. Appl. Math., 2:482 (1981), by the sequence identity alignment algorithm of Needleman & Wunsch, J. Mol. Biol., 48:443 (1970), by the search for similarity method of Pearson & Lipman, Proc. Natl. Acad. Sci. U.S.A., 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Drive, Madison, Wis.), the Best Fit sequence program described by Devereux et al., Nucl. Acid Res., 12:387-395 (1984), preferably using the default settings, or by inspection. Preferably, percent identity is calculated by FastDB based upon the following parameters: mismatch penalty of 1; gap penalty of 1; gap size penalty of 0.33; and joining penalty of 30, "Current Methods in Sequence Comparison and Analysis," Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp 127-149 (1988), Alan R. Liss, Inc, all of which are incorporated by reference.

[0223] An example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pair wise alignments. It may also plot a tree showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng & Doolittle, J. Mol. Evol. 35:351-360 (1987); the method is similar to that described by Higgins & Sharp CABIOS 5:151-153 (1989), both incorporated by reference. Useful PILEUP parameters including a default gap weight of 3.00, a default gap length weight of 0.10, and weighted end gaps.

[0224] Another example of a useful algorithm is the BLAST algorithm, described in: Altschul et al., J. Mol. Biol. 215, 403-410, (1990); Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997); and Karlin et al., Proc. Natl. Acad. Sci. U.S.A. 90:5873-5787 (1993), both incorporated by reference. A particularly useful BLAST program is the WU-BLAST-2 program which was obtained from Altschul et al., Methods in Enzymology, 266:460-480 (1996); http://blast.wustl/edu/blast/README.html]. WU-BLAST-2 uses several search parameters, most of which are set to the default values. The adjustable parameters are set with the following values: overlap span=1, overlap fraction=0.125, word threshold (T)=11. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched; however, the values may be adjusted to increase sensitivity.

[0225] An additional useful algorithm is gapped BLAST, as reported by Altschul et al., Nucl. Acids Res., 25:3389-3402, incorporated by reference. Gapped BLAST uses BLOSUM-62 substitution scores; threshold T parameter set to 9; the two-hit method to trigger ungapped extensions; charges gap lengths of k a cost of 10+k; Xu set to 16, and Xg set to 40 for database search stage and to 67 for the output stage of the algorithms. Gapped alignments are triggered by a score corresponding to ~22 bits.

[0226] A % amino acid sequence identity value is determined by the number of matching identical residues divided by the total number of residues of the "longer" sequence in the aligned region. The "longer" sequence is the one having the most actual residues in the aligned region (gaps introduced by WU-Blast-2 to maximize the alignment score are ignored). In a similar manner, "percent (%) nucleic acid sequence identity" with respect to the coding sequence of the polypeptides identified is defined as the percentage of nucleotide residues in a candidate sequence that are identical with the nucleotide residues in the coding sequence of the cell cycle protein. A preferred method utilizes the BLASTN module of WU-BLAST-2 set to the default parameters, with overlap span and overlap fraction set to 1 and 0.125, respectively.

[0227] The alignment may include the introduction of gaps in the sequences to be aligned. In addition, for sequences which contain either more or fewer amino acids than the protein encoded by the sequence of FIG. **2** (SEQ ID NO:1), it is understood that in one embodiment, the percentage of sequence identity will be determined based on the number of identical amino acids or nucleotides in relation to the total number of amino acids or nucleotides. Thus, for example, sequence identity of sequences shorter than that shown in FIG. **2** (SEQ ID NO:1), as discussed below, will be determined using the number of nucleotides in the shorter sequence, in one embodiment. In percent identity calculations relative weight is not assigned to various manifestations of sequence variation, such as, insertions, deletions, substitutions, etc.

[0228] In one embodiment, only identities are scored positively (+1) and all forms of sequence variation including

gaps are assigned a value of "0", which obviates the need for a weighted scale or parameters as described below for sequence similarity calculations. Percent sequence identity may be calculated, for example, by dividing the number of matching identical residues by the total number of residues of the "shorter" sequence in the aligned region and multiplying by 100. The "longer" sequence is the one having the most actual residues in the aligned region.

[0229] The term "allelic variants" refers to polymorphic forms of a gene at a particular genetic locus, as well as cDNAs derived from mRNA transcripts of the genes, and the polypeptides encoded by them. The term "preferred mammalian codon" refers a subset of codons from among the set of codons encoding an amino acid that are most frequently used in proteins expressed in mammalian cells as chosen from the following list: Gly (GGC, GGG); Glu (GAG); Asp (GAC); Val (GTG, GTC); Ala (GCC, GCT); Ser (AGC, TCC); Lys (AAG); Asn (AAC); Met (ATG); Ile (ATC); Thr (ACC); Trp (TGG); Cys (TGC); Tyr (TAT, TAC); Leu (CTG); Phe (TTC); Arg (CGC, AGG, AGA); Gln (CAG); His (CAC); and Pro (CCC).

[0230] As used herein, the term codon-altered refers to a polynucleotide sequence encoding a polypeptide (e.g., a Factor VIII variant protein), where at least one codon of the native polynucleotide encoding the polypeptide has been changed to improve a property of the polynucleotide sequence. In some embodiments, the improved property promotes increased transcription of mRNA coding for the polypeptide, increased stability of the mRNA (e.g., improved mRNA half-life), increased translation of the polypeptide, and/or increased packaging of the polynucleotide within the vector. Non-limiting examples of alterations that can be used to achieve the improved properties include changing the usage and/or distribution of codons for particular amino acids, adjusting global and/or local GC content, removing AT-rich sequences, removing repeated sequence elements, adjusting global and/or local CpG dinucleotide content, removing cryptic regulatory elements (e.g., TATA box and CCAAT box elements), removing of intron/exon splice sites, improving regulatory sequences (e.g., introduction of a Kozak consensus sequence), and removing sequence elements capable of forming secondary structure (e.g., stem-loops) in the transcribed mRNA.

[0231] As discussed herein, there are various nomenclatures to refer to components of the disclosure herein. "CS-number" (e.g. "CS04", "CS01", "CS23", etc.) refer to codon altered polynucleotides encoding FVIII polypeptides and/or the encoded polypeptides, including variants. For example, CS01-FL refers to the Full Length codon altered CS01 polynucleotide sequence or amino acid sequence (sometimes referred to herein as "CS01-FL-AA" for the Amino Acid sequence and "CS01-FL-NA" for the Nucleic Acid sequence) encoded by the CS01 polynucleotide sequence. Similarly, "CS01-LC" refers to either the codon altered nucleic acid sequence ("CS01-LC-NA") encoding the light chain of a FVIII polypeptide or the amino acid sequence (also sometimes referred to herein as "CS01-LC-AA") of the FVIII light chain encoded by the CS01 polynucleotide sequence. Likewise, CS01-HC, CS01-HC-AA and CS01-HC-NA are the same for the FVIII heavy chain. As will be appreciated by those in the art, for constructs such as CS01, CS04, CS23, etc., that are only codon-altered (e.g. they do not contain additional amino acid substitutions as compared to Refacto), the amino acid sequences will be identical, as the amino acid sequences are not altered by the codon optimization. Thus, sequence constructs of the disclosure include, but are not limited to, CS01-FL-NA, CS01-FL-AA, CS01-LC-NA, CS01-LC-AA, CS01-HC-AA, CS01-HC-NA, CS04-FL-NA, CS04-FL-AA, CS04-LC-NA, CS04-LC-AA, CS04-HC-AA, CS04-HC-NA, CS23-FL-NA, CS23-FL-AA, CS23-LC-NA, CS23-LC-AA, CS23-HC-AA and CS23-HC-NA.

[0232] This nomenclature also applies to glycosylation peptides as shown in FIG. **13**, such that "NGA1-AA" refers to the amino acid sequence and NGA1-NA refers to the nucleic acid sequence.

[0233] The disclosure also includes additional new Factor VIII variants, as described below, with the appropriate nomenclature.

III. Codon-Altered Factor VIII Variants

[0234] In some embodiments, the present disclosure provides codon-altered polynucleotides encoding Factor VIII variants. These codon-altered polynucleotides provide markedly improved expression of Factor VIII when administered in an AAV-based gene therapy construct. The codon-altered polynucleotides also demonstrate improved AAV-virion packaging, as compared to conventionally codon-optimized constructs. As demonstrated in Example 2 and Example 4, Applicants have achieve these advantages through the discovery of three codon-altered polynucleotides (CS01-FL-NA, CS04-FL-NA, and CS23-FL-NA) encoding a Factor VIII polypeptide with human wild-type Factor VIII heavy and light chains, and a short, 14 amino acid, B-domain substituted linker (the "SQ" linker) containing a furin cleavage site to facilitate maturation of an active FVIIIa protein in vivo. As further demonstrated in Example 4, incorporation of various combinations of the F328S, X5, and X1 amino acid mutations into the encoded Factor VIII molecule further increased the in vivo expression of Factor VIII activity.

[0235] In one embodiment, a codon-altered polynucleotide provided herein has nucleotide sequences with high sequence identity to at least the sequences within CS01, CS04, or CS23 (SEQ ID NOS 13, 1, and 20, respectively) encoding the Factor VIII heavy chain and Factor VIII light chains. As known in the art, the B-domain of Factor VIII is dispensable for activity in vivo. Thus, in some embodiments, the codon-altered polynucleotides provided herein completely lack a Factor VIII B-domain. In some embodiments, the native Factor VIII B-domain is replaced with a short amino acid linker containing a furin cleavage site, e.g., the "SQ" linker consisting of amino acids 760-773 of the CS01, CS04, or CS23 (SEQ ID NOS 2, 2, and 21, respectively) constructs. The "SQ" linker is also referred to as BDLO4, (−AA for the amino acid sequence and −NA for the nucleotide sequence shown in FIG. **6**).

[0236] In one embodiment, the Factor VIII heavy and light chains encoded by the codon-altered polynucleotide are human Factor VIII heavy and light chains, respectively. In other embodiments, the Factor VIII heavy and light chains encoded by the codon-altered polynucleotide are heavy and light chain sequences from another mammal (e.g., porcine Factor VIII). In yet other embodiments, the Factor VIII heavy and light chains are chimeric heavy and light chains (e.g., a combination of human and a second mammalian sequence). In yet other embodiments, the Factor VIII heavy and light chains are humanized version of the heavy and

light chains from another mammal, e.g., heavy and light chain sequences from another mammal in which human residues are substituted at select positions to reduce the immunogenicity of the resulting peptide when administered to a human.

[0237] The GC content of human genes varies widely, from less than 25% to greater than 90%. However, in general, human genes with higher GC contents are expressed at higher levels. For example, Kudla et al. (PLoS Biol., 4(6):80 (2006)) demonstrate that increasing a gene's GC content increases expression of the encoded polypeptide, primarily by increasing transcription and effecting a higher steady state level of the mRNA transcript. Generally, the desired GC content of a codon-optimized gene construct is equal or greater than 60%. However, native AAV genomes have GC contents of around 56%.

[0238] Accordingly, in some embodiments, the codon-altered polynucleotides provided herein have a CG content that more closely matches the GC content of native AAV virions (e.g., around 56% GC), which is lower than the preferred CG contents of polynucleotides that are conventionally codon-optimized for expression in mammalian cells (e.g., at or above 60% GC). As outlined in Example 1, CS04-FL-NA (SEQ ID NO: 1), which has a GC content of about 56%, has improved virion packaging as compared to similarly codon-altered coding sequences with higher GC content.

[0239] Thus, in some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is less than 60%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is less than 59%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is less than 58%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is less than 57%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is no more than 56%.

[0240] In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 54% to 59%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 55% to 59%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 56% to 59%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 54% to 58%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 55% to 58%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 56% to 58%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 54% to 57%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 55% to 57%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 56% to 57%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 54% to 56%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is from 55% to 56%.

[0241] In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is 56±0.5%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is 56±0.4%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is 56±0.3%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is 56±0.2%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is 56±0.1%. In some embodiments, the overall GC content of a codon-altered polynucleotide encoding a Factor VIII polypeptide is 56%.

[0242] A. Factor VIII Amino Acid Substitutions

[0243] To further increase the efficiency of AAV-vector based expression of the Factor VIII constructs described herein, amino acid substitutions know to improve secretion, increase specific activity, and/or enhanced the stability of Factor VIII are further incorporated, in some implementations. A number of potential variants were identified that increase the plasma levels of FVIII activity at a given vector dose. These variants include those with a more efficient signal peptide, amino acid substitutions that prevent BiP interactions, amino acid substitutions resembling more efficiently secreted Factor VIII orthologs (e.g., porcine Factor VIII), single-chain Factor VIII variants, and amino acid substitutions that stabilize Factor VIII and/or reduce subunit dissociation.

[0244] Mutation of residues A108, R121, and L2302 (SPE), located at the interface between the A1 and C2 domains, increases the stability of Factor VIII. For example, the A108I amino acid substitution introduces a hydrophobic residue that better fills the inter-domain space, stabilizing the interaction. Likewise, an R121C/L2302C (SPE) double amino acid substitution introduces a disulfide bond spanning the A1-C2 domains, further stabilizing the interaction. Taken together, all three amino acid substitutions increase the thermal stability of Factor VIII by 3 to 4-fold. For review, see Wakabayashi et al., J Biol Chem. 286(29):25748-55 (2011) and Wakabayashi et al., Thromb Haemost. 10(3): 492-95 (2012). Accordingly, in some embodiments, the encoded Factor VIII polypeptide includes A108I and/or R121C/L2302C amino acid substitutions.

[0245] Mutation of E113 (SPE), located within the calcium binding domain of Factor VIII, increases the specific FVIII clotting activity. For example, E113A appears to increase FXase formation through increased FVIII affinity for Factor IXa. Specifically, the E113A amino acid substitution increases specific FVIII clotting activity two-fold and increases affinity for Factor IXa by four-fold (Biochemistry, 41:8485 (2002); J. Biol. Chem., 279:12677 (2004); and Biochemistry, 44:10298 (2005)). Accordingly, in some embodiments, the encoded Factor VIII polypeptides include an E113A amino acid substitution.

[0246] Substitution of one or more amino acid residues surrounding the Factor VIII APC cleavage site (residues 331-341 (SPE)) reduce Factor VIIIa inactivation by activated protein C, without affecting FVIII activity. For example PQL333-335VDQ (SPE) amino acid substitutions reduce Factor VIII inactivation by 16-fold. Likewise, MKN336-339GNQ amino acid substitutions reduce Factor

VIII inactivation by 9-fold. When combined, the two triple amino acid substitutions (e.g., PQLRMKN333-339VDQRGNQ) (SEQ ID NOS 34 and 35, respectively) reduce Factor VIII inactivation by 100-fold (J. Biol. Chem., 282:20264 (2007). Accordingly, in some embodiments, the encoded Factor VIII polypeptide include PQL333-335VDQ and/or MKN337-339GNQ (SPE) amino acid substitutions.

[0247] Mutations within the A2 domain interface also increase Factor VIII stability. Specifically, mutating charged residues in the A1-A2 and A2-A3 domain interfaces increases stability and retention of the A2 subunit in Factor VIIIa. For example, mutation of D519, E665, and E1984 to V or A yields up to 2-fold increased stability in Factor VIII and up to 5-fold stability in Factor VIIIa. Specifically, D519A/E665V amino acid substitutions provide a 3-fold increase in stability; D519V/E665V amino acid substitutions provide a 2-fold increase in stability, an 8-fold decrease in A2 dissociation, and a 2-4-fold increase in thrombin generation potential; D519V/E1984A amino acid substitutions provide a 2-fold increase in stability; and D519V/E665V/E1984A amino acid substitution provide a 2-fold increase in stability (Blood 112:2761-69 (2008); J. Thromb. Haemost., 7:438-44 (2009)). Accordingly, in some embodiments, the encoded Factor VIII polypeptides include one or more of D519A/V, E665A/V, and E1984A/V amino acid substitutions.

[0248] Of particular relevance to the present disclosure are a number of specific mutations that can be included separately or in combinations with other variants described herein. These variants are coded as sets herein as follows: "m1" refers to a single amino acid change, "m2" is a set of 5 amino acid variants, "m3" is a combination of a deletion of 7 amino acids and an insertion of six amino acids that span the junction between the polypeptide linker and the heavy chain, "m4" is a combination of the m1 single mutation and the m5 double mutation, and "m5" is a set of two cysteine ablations. These mutations are described below. These can be included in any particular construct alone or in combination with other variants, and they are coded accordingly. For example, "m23" is a combination of the m2 and m3 variants onto a particular scaffold, as outlined herein; thus "CS01m23-FL-NA" or "CS01-FL-NAm23" refers to the CS01 codon-altered polynucleotide sequence with the nucleotides encoding the m2 and m3 mutations included, and "CS01m23-FL-AA" or "CS01-FL-AAm23" refers to the amino acid sequence. As CS01 is codon-altered but does not change the amino acid sequence of Refacto, these can be thought of on the amino acid level as mutations as compared to the Refacto amino acid sequence of CS01-FL-AA (SEQ ID NO: 2).

[0249] In many embodiments, the polypeptides of the disclosure are made with the "m1" variant included. Mutations within an 11 amino acid hydrophobic β-sheet in the A1 domain, which interacts with BiP, increase secretion of Factor VIII. For example, an F328S (SPI, F309S SPE) amino acid substitution within the pocket increased Factor VIII secretion 3-fold. The F328S variant is referred to herein as the "m1" mutation and is within the heavy chain. Again, as described herein, the number of the variants can be done inclusive of the signal peptide, "Signal Peptide Inclusive", or "SPI", or starting from the processed final protein sequence, "Signal Peptide Exclusive", or "SPE". Thus, using SPI numbering, the mutation F328S is the same as the F309 SPE mutant. Generally the specification uses the SPI numbering, but as will be appreciated by those in the art, either numbering system results in the same mutation(s).

[0250] Accordingly, included in the present disclosure are polypeptides that include the m1 mutation, including CS01-FL-AAm1, CS01-HC-AAm1, CS04-FL-AAm1, CS04-HC-AAm1 CS23-FL-AAm1, CS23-HC-AAm1, CS40-FL-AAm1 and CS40-HC-AAm1 (all of which encode the same corresponding protein sequences).

[0251] In addition, included in the present disclosure are not only polypeptide sequences that include the m1 mutation, but also those codon-altered polynucleotide sequences that encode proteins with the m1 mutation, such as CS01-FL-NAm1, CS01-HC-NAm1, CS04-FL-NAm1, CS04-HC-NAm1, CS23-FL-NAm1, CS23-HC-NA-m1, CS40-FL-NAm1 and CS40-HC-NAm1.

[0252] In many embodiments, the polypeptides of the disclosure are made with the "m2" variant set included, which is the I105V/A127S/G151K/M166T/L171P mutations (SPI numbering; (SPE numbering is V861/S108A/K132G/T147M/P152L, respectively). The m2 mutation set is based on the fact that substitution of porcine amino acids 82-176 for the corresponding human amino acids in a B-domain deleted gene therapy construct increased Factor VIII activity when expressed in HEK293 cells (W. Xiao, communication). Id. Back-mutation of single porcine amino acids into the human BDD-FVIII construct identified five amino acids within the A1 domain that contribute to this phenomenon: I105V, A127S, G151K, M166T, and L171P (SPI). Introduction of the combination of these mutations into the human construct recapitulated the improved activity of the larger porcine substitution. Id. Accordingly, in some embodiments, the encoded Factor VIII polypeptides include one or more amino acid substitutions selected from I105V, A127S, G151K, M166T, and L171P, with the entire 5 amino acid set, m2, finding particular use in many embodiments. As for the m1 mutation, the m2 variants are in the heavy chain, and thus the present disclosure includes polypeptides that include the m2 mutation, including CS01-FL-AAm2, CS01-HC-AAm2, CS04-FL-AAm2, CS04-HC-AAm2, CS23-FL-AAm2, CS23-HC-AAm2, CS40-FL-AAm2 and CS40-HC-AAm2 (all of which encode the same corresponding protein sequences).

[0253] In addition, included in the present disclosure are not only polypeptide sequences that include the m2 mutation, but also those codon-altered polynucleotide sequences that encode proteins with the m2 mutation, such as CS01-FL-NAm2, CS01-HC-NAm2, CS04-FL-NAm2, CS04-HC-NAm2, CS23-FL-NAm2, CS23-HC-NA-m2, CS40-FL-NAm2 and CS40-HC-NAm2.

[0254] In additional embodiments, the polypeptides and polynucleotides of the disclosure include m3 mutations. m3 is the substitution of seven amino acids for six across the HC-B domain interface that introduces an additional glycosylation site introduced close to the interface. Accordingly, in some embodiments, m3 is the deletion of amino acids AIEPRSF755-761 and the insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19) (e.g., AIEPRSF755-761TTYVNRSL) ("TTYVNRSL" disclosed as SEQ ID NO: 33). Residues AIEPR755-759, relative to SEQ ID NO: 19, fall within the end of the heavy chain, while residues 5760 and F761 fall within the B-domain. In some embodiments, where the FVIII B-domain is deleted, truncated, or replaced, residues 5760 and F761 may not be present in the underlying

amino acid sequence being mutated. Accordingly, in some embodiments, m3 is the deletion of amino acids AIEPR755-759 and the insertion of amino acids TTYVNRSL (SEQ ID NO: 33) after N754, relative to FVIII-FL-AA (SEQ ID NO: 19) (e.g., AIEPR755-759TTYVNRSL ("TTYVNRSL" disclosed as SEQ ID NO: 33)

[0255] The m3 variants are in the junction between the heavy chain and the B domain, and thus the present disclosure includes polypeptides that include the m3 mutation, including CS01-FL-AAm3, CS01-HC-AAm3, CS04-FL-AAm3, CS04-HC-AAm3, CS23-FL-AAm3, CS23-HC-AAm3, CS40-FL-AAm3 and CS40-HC-AAm3 (all of which encode the same corresponding protein sequences).

[0256] In addition, included in the present disclosure are not only polypeptide sequences that include the m3 mutation, but also those codon-altered polynucleotide sequences that encode proteins with the m3 mutations, such as CS01-FL-NAm3, CS01-HC-NAm3, CS04-FL-NAm3, CS04-HC-NAm3, CS23-FL-NAm3, CS23-HC-NA-m3, CS40-FL-NAm3 and CS40-HC-NAm3.

[0257] In additional embodiments, the polypeptides and polynucleotides of the disclosure include m4 mutations. Elimination of the C1899-C1903 disulfide bond in Factor VIII also increased secretion. Moreover, the increases in Factor VIII secretion are additive for the combination of F328S (SPI, F309S SPE) and C1918G/C1922G amino acid substitutions (Miao et al., Blood, 103:3412-19 (2004); Selvaraj et al., J. Thromb. Haemost., 10:107-15 (2012)). Accordingly, in some embodiments, the encoded Factor VIII polypeptides include m4 mutations, which is the F328S (SPI, F309S SPE) and C1918G/C1922G (SPI) amino acid substitutions. As the F328S variant is in the heavy chain and the two cysteine variants are in the light chain, polypeptide sequences that include m4 mutations are CS01-FL-AAm4, CS01-HC-AAm4, CS01-LC-AAm4, CS04-FL-AAm4, CS04-HC-AAm4, CS04-LC-AAm4, CS23-FL-AAm4, CS23-HC-AAm4 and CS23-LC-AAm4.

[0258] In addition, included in the present disclosure are not only polypeptide sequences that include the m4 mutation, but also those codon-altered polynucleotide sequences that encode proteins with the m4 mutations, such as CS01-FL-NAm4, CS01-HC-NAm4, CS01-LC-NAm4, CS04-FL-NAm4, CS04-HC-NAm4, CS04-LC-NAm4, CS23-FL-NAm4, CS23-HC-NAm4, CS23-LC-NAm4, CS40-FL-NA-m4, CS40-HC-NA-m4 and CS40-LC-NA-m4.

[0259] In additional embodiments, the polypeptides and polynucleotides of the disclosure include m5 mutations. As above, elimination of the C1899-C1903 disulfide bond in Factor VIII also increased secretion. C1918G/C1922G (SPI) amino acid substitutions, contained within the light chain, referred to herein as the m5 mutation set.

[0260] The m5 variants are in the light chain, and thus the present disclosure includes polypeptides that include the m5 mutation, including CS01-FL-AAm5, CS01-LC-AAm5, CS04-FL-AAm5, CS04-LC-AAm5, CS23-FL-AAm5, CS23-LC-AAm5, CS40-FL-AAm5 and CS40-LC-AAm5 (all of which encode the same corresponding protein sequences).

[0261] In addition, included in the present disclosure are not only polypeptide sequences that include the m5 mutation, but also those codon-altered polynucleotide sequences that encode proteins with the m5 mutations, such as CS01-FL-NAm5, CS01-LC-NAm5, CS04-FL-NAm5, CS04-LC-NAm5, CS23-FL-NA-m5, CS23-LC-NA-m5, CS40-FL-NA-m5 and CS40-LC-NA-m5.

[0262] In addition to specific constructs (both amino acid and nucleic acid) that include m1, m2, m3, m4 and m5 individually, combinations of mutation sets can be made as outlined herein. As noted herein, these are noted as "m12", which is the combination of m1 and m2 sets, or "m123" which is the combination of m1, m2 and m3 sets. Thus, included in the disclosure are dual combinations including m12, m13, m14, m15, m23, m24, m25, m34, m35 and m45. Also included are triple combinations, m123, m124, m125, m234, m235 and m345. Further included are quad combinations, m1234, m1235, m1345 and the m12345 combination. Of particular interest in some embodiments are the following mutation sets: m1, m2, m3 and m4, m23, m123, and m234.

[0263] B. Factor VIII B-Domain Substituted Linkers

[0264] In some embodiments, the linkage between the FVIII heavy chain and the light chain (e.g., the B-domain in wild-type Factor VIII) is further altered. Due to size constraints of AAV packaging capacity, B-domain deleted, truncated, and or linker substituted variants should improve the efficacy of the FVIII gene therapy construct. The most conventionally used B-domain substituted linker is that of SQ FVIII, which retains only 14 amino acids of the B domain as linker sequence. Another variant of porcine VIII ("OBI-1," described in U.S. Pat. No. 6,458,563) is well expressed in CHO cells, and has a slightly longer linker of 24 amino acids. In some embodiments, the Factor VIII constructs encoded by the codon-altered polynucleotides described herein include an SQ-type B-domain linker sequence. In other embodiments, the Factor VIII constructs encoded by the codon-altered polynucleotides described herein include an OBI-1-type B-domain linker sequence.

[0265] In some embodiments, the encoded Factor VIII polypeptides described herein include an SQ-type B-domain linker, including amino acids 760-762/1657-1667 of the wild-type human Factor VIII B-domain (FVIII-FL-AA; SEQ ID NO: 19) (Sandberg et al. Thromb. Haemost. 85:93 (2001)). In some embodiments, the SQ-type B-domain linker has one amino acid substitution relative to the corresponding wild-type sequence. In some embodiments, the SQ-type B-domain linker has two amino acid substitutions relative to the corresponding wild-type sequence. In some embodiments, a glycosylation peptide is inserted into the SQ-type B-domain linker. In some embodiments, the glycosylation peptide is selected from those shown in FIG. **13** (SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance).

[0266] In some embodiments, the encoded Factor VIII polypeptides described herein include a Greengene-type B-domain linker, including amino acids 760/1582-1667 of the wild-type human Factor VIII B-domain (FVIII-FL-AA; SEQ ID NO: 19) (Oh et al., Biotechnol. Prog., 17:1999 (2001)). In some embodiments, the Greengene-type B-domain linker has one amino acid substitution relative to the corresponding wild-type sequence. In some embodiments, the Greengene-type B-domain linker has two amino acid substitutions relative to the corresponding wild-type sequence. In some embodiments, a glycosylation peptide is inserted into the Greengene-type B-domain linker. In some embodiments, the glycosylation peptide is selected from

those shown in FIG. **13** (SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance).

[0267] In some embodiments, the encoded Factor VIII polypeptides described herein include an extended SQ-type B-domain linker (SFSQNPPVLKRHQR; BDL-SQ-AA; SEQ ID NO: 30), including amino acids 760-769/1657-1667 of the wild-type human Factor VIII B-domain (FVIII-FL-AA; SEQ ID NO: 19) (Thim et al., Haemophilia, 16:349 (2010)). In some embodiments, the extended SQ-type B-domain linker has one amino acid substitution relative to the corresponding wild-type sequence. In some embodiments, the extended SQ-type B-domain linker has two amino acid substitutions relative to the corresponding wild-type sequence. In some embodiments, a glycosylation peptide is inserted into the extended SQ-type B-domain linker. In some embodiments, the glycosylation peptide is selected from those shown in FIG. **13** (SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance).

[0268] In some embodiments, the encoded Factor VIII polypeptides described herein include a porcine OBI-1-type B-domain linker, including the amino acids SFAQNSRPPSASAPKPPVLRRHQR (SEQ ID NO: 31) from the wild-type porcine Factor VIII B-domain (Toschi et al., Curr. Opin. Mol. Ther. 12:517 (2010)). In some embodiments, the porcine OBI-1-type B-domain linker has one amino acid substitution relative to the corresponding wild-type sequence. In some embodiments, the porcine OBI-1-type B-domain linker has two amino acid substitutions relative to the corresponding wild-type sequence. In some embodiments, a glycosylation peptide is inserted into the porcine OBI-1-type B-domain linker. In some embodiments, the glycosylation peptide is selected from those shown in FIG. **13** (SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance).

[0269] In some embodiments, the encoded Factor VIII polypeptides described herein include a human OBI-1-type B-domain linker, including amino acids 760-772/1655-1667 of the wild-type human Factor VIII B-domain (FVIII-FL-AA; SEQ ID NO: 19). In some embodiments, the human OBI-1-type B-domain linker has one amino acid substitution relative to the corresponding wild-type sequence. In some embodiments, the human OBI-1-type B-domain linker has two amino acid substitutions relative to the corresponding wild-type sequence. In some embodiments, a glycosylation peptide is inserted into the human OBI-1-type B-domain linker. In some embodiments, the glycosylation peptide is selected from those shown in FIG. **13** (SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance).

[0270] In some embodiments, the encoded Factor VIII polypeptides described herein include an 08-type B-domain linker, including the amino acids SFSQNSRHQAYRYRRG (SEQ ID NO: 32) from the wild-type porcine Factor VIII B-domain (Toschi et al., Curr. Opin. Mol. Ther. 12:517 (2010)). In some embodiments, the porcine OBI-1-type B-domain linker has one amino acid substitution relative to the corresponding wild-type sequence. In some embodiments, the porcine OBI-1-type B-domain linker has two amino acid substitutions relative to the corresponding wild-type sequence. In some embodiments, a glycosylation peptide is inserted into the porcine OBI-1-type B-domain linker. In some embodiments, the glycosylation peptide is selected from those shown in FIG. **13** (SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance).

[0271] Removal of the B-domain from Factor VIII constructs does not appear to affect the activity of the activated enzyme (e.g., FVIIIa), presumably because the B-domain is removed during activation. However, the B-domain of Factor VIII contains several residues that are post-translationally modified, e.g., by N- or O-linked glycosylation. In silico analysis (Prediction of N-glycosylation sites in human proteins, R. Gupta, E. Jung and S. Brunak, in preparation (2004)) of the wild-type Factor VIII B-domain predicts that at least four of these sites are glycosylated in vivo (FIG. **14**). It is thought that these modifications within the B-domain contribute to the post-translational regulation and/or half-life of Factor VIII in vivo.

[0272] While the Factor VIII B-domain is absent in mature Factor VIIIa protein, glycosylation within the B-domain of the precursor Factor VIII molecule may increase the circulating half-life of the protein prior to activation. Thus, in some embodiments, the polypeptide linker of the encoded Factor VIII constructs described herein includes one or more glycosylation sequences, to allow for glycosylation in vivo. In some embodiments, the polypeptide linker includes at least one consensus glycosylation sequence (e.g., an N- or O-linked glycosylation consensus sequence). In some embodiments, the polypeptide linker includes at least two consensus glycosylation sequences. In some embodiments, the polypeptide linker includes at least three consensus glycosylation sequences. In some embodiments, the polypeptide linker includes at least four consensus glycosylation sequences. In some embodiments, the polypeptide linker includes at least five consensus glycosylation sequences. In some embodiments, the polypeptide linker includes at least 6, 7, 8, 9, 10, or more consensus glycosylation sequences.

[0273] In some embodiments, the polypeptide linker contains at least one N-linked glycosylation sequence N-X-S/T, where X is any amino acid other than P, S, or T. In some embodiments, the polypeptide linker contains at least two N-linked glycosylation sequences N-X-S/T, where X is any amino acid other than P, S, or T. In some embodiments, the polypeptide linker contains at least three N-linked glycosylation sequences N-X-S/T, where X is any amino acid other than P, S, or T. In some embodiments, the polypeptide linker contains at least four N-linked glycosylation sequences N-X-S/T, where X is any amino acid other than P, S, or T. In some embodiments, the polypeptide linker contains at least five N-linked glycosylation sequences N-X-S/T, where X is any amino acid other than P, S, or T. In some embodiments, the polypeptide linker contains at least 6, 7, 8, 9, 10, or more N-linked glycosylation sequences N-X-S/T, where X is any amino acid other than P, S, or T.

[0274] In some embodiments, the polypeptide linker includes a glycosylation peptide with high sequence identity to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation polypeptide has at least 92% identity to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has no more than two amino acid substitutions relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order

of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has no more than one amino acid substitution relative to any of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has an amino acid sequence selected from any of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B.

[0275] In some embodiments, the glycosylation peptide has at least 92% identity to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 90% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has at least 92% identity to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 95% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has at least 92% identity to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 98% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B.

[0276] In some embodiments, the glycosylation peptide has no more than two amino acid substitutions relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B, and is encoded by a polynucleotide sequence having at least 90% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has no more than two amino acid substitutions relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B, and is encoded by a polynucleotide sequence having at least 95% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has no more than two amino acid substitutions relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B, and is encoded by a polynucleotide sequence having at least 98% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B.

[0277] In some embodiments, the glycosylation peptide has no more than one amino acid substitution relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 90% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has no more than one amino acid substitution relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 95% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has no more than one amino acid substitution relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 98% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B.

[0278] In some embodiments, the glycosylation peptide has a sequence selected from any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 90% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has a sequence selected from any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 95% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide has a sequence selected from any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B and is encoded by a polynucleotide sequence having at least 98% identity to a corresponding nucleotide sequence selected from SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B.

[0279] In some embodiments, the Factor VIII polypeptide encoded by a codon-altered polynucleotide described herein has a B-domain substituted linker in which a glycosylation peptide is inserted into the SQ linker sequence (amino acids 760-773 of CS04-FL-AA; SEQ ID NO: 2). In a specific embodiment, the glycosylation peptide is selected from selected from any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B, a glycosylation peptide having at least 92% identity to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B, a glycosylation peptide having no more than two

amino acid substitutions relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B, and a glycosylation peptide having no more than one amino acid substitution relative to any one of SEQ ID NOS 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, and 75, respectively, in order of appearance, as shown in FIGS. **13**A-**13**B. In some embodiments, the glycosylation peptide is inserted in the SQ peptide between residues N768 and P769 (relative to CS04-FL-AA; SEQ ID NO: 2).

[0280] In some embodiments, the polypeptide linker of the Factor VIII construct is encoded by a third nucleotide sequence having high sequence identity to any one of those shown in FIG. **6** (SEQ ID NOS 5-7 and 36-48, respectively, in order of appearance). In some embodiments, the third nucleotide sequence has at least 95% identity to any one of those shown in FIG. **13** (SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance). In some embodiments, the third nucleotide sequence has at least 96% identity to any one of those shown in FIG. **13** (SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance). In some embodiments, the third nucleotide sequence has at least 97% identity to any one of those shown in FIG. **13** (SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance). In some embodiments, the third nucleotide sequence has at least 98% identity to any one of those shown in FIG. **13** (SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance). In some embodiments, the third nucleotide sequence has at least 99% identity to any one of those shown in FIG. **13** (SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance). In some embodiments, the third nucleotide sequence has at least 99.5% identity to any one of those shown in FIG. **13** (SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance). In some embodiments, the third nucleotide sequence has at least 99.9% identity to any one of those shown in FIG. **13** (SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance). In some embodiments, the third nucleotide sequence is identical to any one of those shown in FIG. **13** (SEQ ID NOS 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, and 74, respectively, in order of appearance).

[0281] C. Codon-Altered Polynucleotides Encoding a Factor VIII Variant with a Cleavable Linker

[0282] CS04 Codon Altered Polynucleotides

[0283] In one embodiment, the codon-altered polynucleotides provided herein include a nucleotide sequence encoding a Factor VIII variant polypeptide with a linker that is cleavable in vivo. The Factor VIII polypeptide includes a Factor VIII light chain, a Factor VIII heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having high sequence identity to CS04-HC-NA (SEQ ID NO: 3), which is the portion of CS04-FL-NA (SEQ ID NO: 1) encoding for a Factor VIII heavy chain. The light chain of the Factor VIII polypeptide is encoded by a second nucleotide sequence with high sequence identity to CS04-LC-NA (SEQ ID NO: 4), which is the portion of CS04-FL-NA (SEQ ID NO: 1) encoding for a Factor VIII light chain. The polypeptide linker includes a furin cleavage site, which allows for maturation in vivo (e.g., after expression in vivo or administration of the precursor polypeptide).

[0284] In some embodiments, the first and second nucleotide sequences have at least 95% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 96% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 97% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 98% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 99% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.5% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.9% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences are identical to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively.

[0285] In some embodiments, the polypeptide linker of the Factor VIII construct is encoded by a third nucleotide sequence having high sequence identity to BDLO04 (SEQ ID NO: 6), which encodes the 14-amino acid linker corresponding to amino acids 760-773 of CS04-FL-AA (SEQ ID NO: 2). In some embodiments, the third nucleotide sequence has at least 95% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 96% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 97% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 98% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence is identical to BDLO04 (SEQ ID NO: 6).

[0286] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS04-FL-NA (SEQ ID NO: 1). In some embodiments, the nucleotide sequence has at least 95% identity to CS04-FL-NA (SEQ ID NO: 1). In some embodiments, the nucleotide sequence has at least 96% identity to CS04-FL-NA (SEQ ID NO: 1). In some embodiments, the nucleotide sequence has at least 97% identity to CS04-FL-NA (SEQ ID NO: 1). In some embodiments, the nucleotide sequence has at least 98% identity to CS04-FL-NA (SEQ ID NO: 1). In some embodiments, the nucleotide sequence has at least 99% identity to CS04-FL-NA (SEQ ID NO: 1). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS04-FL-NA (SEQ ID NO: 1). In some embodiments, the nucleotide sequence has at least 99.9% identity to CS04-FL-NA (SEQ ID NO: 1). In some embodiments, the nucleotide sequence is identical to CS04-FL-NA (SEQ ID NO: 1).

[0287] In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS04-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 97% identity to CS04-FL-AA (SEQ ID

NO: 2). In some embodiments, the amino acid sequence has at least 98% identity to CS04-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 99% identity to CS04-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 99.5% identity to CS04-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 99.9% identity to CS04-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence is identical to CS04-FL-AA (SEQ ID NO: 2).

[0288] In some embodiments, the Factor VIII variant encoded by the CS04 polynucleotide, having high sequence homology to CS04-FL-AA (e.g., at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0289] In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m1 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m2 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m3 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m4 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m5 amino acid substitution.

[0290] In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m12 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m13 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m23 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m24 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m25 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m34 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m35 amino acid substitutions.

[0291] In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m123 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m234 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m125 amino acid substitutions.

[0292] CS01 Codon Altered Polynucleotides

[0293] In one embodiment, the codon-altered polynucleotides provided herein include a nucleotide sequence encoding a Factor VIII variant polypeptide with a linker that is cleavable in vivo. The Factor VIII polypeptide includes a Factor VIII light chain, a Factor VIII heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having high sequence identity to CS01-HC-NA (SEQ ID NO: 24), which is the portion of CS01-FL-NA (SEQ ID NO: 13) encoding for a Factor VIII heavy chain. The light chain of the Factor VIII polypeptide is encoded by a second nucleotide sequence with high sequence identity to CS01-LC-NA (SEQ ID NO: 25), which is the portion of CS01-FL-NA (SEQ ID NO: 13) encoding for a Factor VIII light chain. The polypeptide linker includes a furin cleavage site, which allows for maturation in vivo (e.g., after expression in vivo or administration of the precursor polypeptide).

[0294] In some embodiments, the first and second nucleotide sequences have at least 95% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 96% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 97% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 98% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 99% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.5% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.9% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences are identical to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively.

[0295] In some embodiments, the polypeptide linker of the Factor VIII construct is encoded by a third nucleotide sequence having high sequence identity to BDLO04 (SEQ ID NO: 6), which encodes the 14-amino acid linker corresponding to amino acids 760-773 of CS01-FL-AA (SEQ ID NO: 2). In some embodiments, the third nucleotide sequence has at least 95% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 96% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 97% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 98% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence is identical to BDLO04 (SEQ ID NO: 6).

[0296] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS01-FL-NA (SEQ ID NO: 13). In some embodiments, the nucleotide sequence has at least 95% identity to CS01-FL-NA (SEQ ID NO: 13). In some embodiments, the nucleotide sequence has at least 96% identity to CS01-FL-NA (SEQ ID NO: 13). In some embodiments, the nucleotide sequence has at least 97% identity to CS01-FL-NA (SEQ ID NO: 13). In some embodiments, the nucleotide sequence has at least 98% identity to CS01-FL-NA (SEQ ID NO: 13). In some embodiments, the nucleotide sequence has at least 99% identity to CS01-FL-NA (SEQ ID NO: 13). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS01-FL-NA (SEQ ID NO: 13). In some embodiments, the nucleotide sequence has at least 99.9% identity to CS01-FL-NA (SEQ ID NO: 13). In some embodiments, the nucleotide sequence is identical to CS01-FL-NA (SEQ ID NO: 13).

[0297] In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino

acid sequence with high sequence identity to CS01-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 97% identity to CS01-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 98% identity to CS01-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 99% identity to CS01-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 99.5% identity to CS01-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence has at least 99.9% identity to CS01-FL-AA (SEQ ID NO: 2). In some embodiments, the amino acid sequence is identical to CS01-FL-AA (SEQ ID NO: 2).

[0298] In some embodiments, the Factor VIII variant encoded by the CS01 polynucleotide, having high sequence homology to CS01-FL-AA (e.g., at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0299] In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m1 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m2 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m3 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m4 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m5 amino acid substitution.

[0300] In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m12 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m13 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m23 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m24 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m25 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m34 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m35 amino acid substitutions.

[0301] In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m123 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m234 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m125 amino acid substitutions.

[0302] CS23 Codon Altered Polynucleotides

[0303] In one embodiment, the codon-altered polynucleotides provided herein include a nucleotide sequence encoding a Factor VIII variant polypeptide with a linker that is cleavable in vivo. The Factor VIII polypeptide includes a Factor VIII light chain, a Factor VIII heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having high sequence identity to CS23-HC-NA (SEQ ID NO: 22), which is the portion of CS23-FL-NA (SEQ ID NO: 20) encoding for a Factor VIII heavy chain. The light chain of the Factor VIII polypeptide is encoded by a second nucleotide sequence with high sequence identity to CS23-LC-NA (SEQ ID NO: 23), which is the portion of CS23-FL-NA (SEQ ID NO: 20) encoding for a Factor VIII light chain. The polypeptide linker includes a furin cleavage site, which allows for maturation in vivo (e.g., after expression in vivo or administration of the precursor polypeptide).

[0304] In some embodiments, the first and second nucleotide sequences have at least 95% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 96% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 97% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 98% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 99% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.5% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.9% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences are identical to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively.

[0305] In some embodiments, the polypeptide linker of the Factor VIII construct is encoded by a third nucleotide sequence having high sequence identity to BDLO04 (SEQ ID NO: 6), which encodes the 14-amino acid linker corresponding to amino acids 760-773 of CS23-FL-AA (SEQ ID NO: 21). In some embodiments, the third nucleotide sequence has at least 95% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 96% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 97% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence has at least 98% identity to BDLO04 (SEQ ID NO: 6). In some embodiments, the third nucleotide sequence is identical to BDLO04 (SEQ ID NO: 6).

[0306] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS23-FL-NA (SEQ ID NO: 20). In some embodiments, the nucleotide sequence has at least 95% identity to CS23-FL-NA (SEQ ID NO: 20). In some embodiments, the nucleotide sequence has at least 96% identity to CS23-FL-NA (SEQ ID NO: 20). In some embodiments, the nucleotide sequence has at least 97% identity to CS23-FL-NA (SEQ ID NO: 20). In some embodiments, the nucleotide sequence has at least 98% identity to CS23-FL-NA (SEQ ID NO: 20). In some embodiments, the nucleotide sequence has at least 99% identity to CS23-FL-NA (SEQ ID NO: 20). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS23-FL-NA (SEQ ID NO: 20). In some embodiments, the nucleotide sequence has at least 99.9% identity to

CS23-FL-NA (SEQ ID NO: 20). In some embodiments, the nucleotide sequence is identical to CS23-FL-NA (SEQ ID NO: 20).

[0307] In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS23-FL-AA (SEQ ID NO: 21). In some embodiments, the amino acid sequence has at least 97% identity to CS23-FL-AA (SEQ ID NO: 21). In some embodiments, the amino acid sequence has at least 98% identity to CS23-FL-AA (SEQ ID NO: 21). In some embodiments, the amino acid sequence has at least 99% identity to CS23-FL-AA (SEQ ID NO: 21). In some embodiments, the amino acid sequence has at least 99.5% identity to CS23-FL-AA (SEQ ID NO: 21). In some embodiments, the amino acid sequence has at least 99.9% identity to CS23-FL-AA (SEQ ID NO: 21). In some embodiments, the amino acid sequence is identical to CS23-FL-AA (SEQ ID NO: 21).

[0308] In some embodiments, the Factor VIII variant encoded by the CS23 polynucleotide, having high sequence homology to CS23-FL-AA (e.g., at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0309] In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m1 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m2 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m3 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m4 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m5 amino acid substitution.

[0310] In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m12 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m13 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m23 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m24 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m25 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m34 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m35 amino acid substitutions.

[0311] In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m123 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m234 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m125 amino acid substitutions.

[0312] D. Codon-Altered Polynucleotides Encoding a Single-Chain Factor VIII Protein

[0313] Factor VIII constructs in which the furin cleavage site located at the C-terminal end of the B-domain is removed retain activity as a single chain polypeptide, despite that normal maturation of the Factor VIII molecule cannot occur (Leyte et al. (1991)). Similarly, a B-domain deleted Factor VIII construct with an attenuated furin site (containing an R1664H amino acid substitution) is more biologically active than the corresponding Factor VIII construct with a wild-type furin cleavage site (Siner et al. (2013)). Accordingly, in some embodiments, the codon-altered polynucleotides provided herein include a nucleotide sequence encoding a single-chain Factor VIII variant polypeptide. The single-chain Factor VIII polypeptide includes a Factor VIII light chain, a Factor VIII heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The polypeptide linker does not include a furin cleavage site.

[0314] Single-Chain CS04 Codon Altered Polynucleotides

[0315] In one embodiment, the codon-altered polynucleotides provided herein include a nucleotide sequence encoding a single-chain Factor VIII variant polypeptide. The Factor VIII polypeptide includes a Factor VIII light chain, a Factor VIII heavy chain, and an optional polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having high sequence identity to CS04-HC-NA (SEQ ID NO: 3), which is the portion of CS04-FL-NA (SEQ ID NO: 1) encoding for a Factor VIII heavy chain. The light chain of the Factor VIII polypeptide is encoded by a second nucleotide sequence with high sequence identity to CS04-LC-NA (SEQ ID NO: 4), which is the portion of CS04-FL-NA (SEQ ID NO: 1) encoding for a Factor VIII light chain. The optional polypeptide linker does not include a furin cleavage site.

[0316] In some embodiments, the first and second nucleotide sequences have at least 95% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 96% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 97% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 98% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 99% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.5% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.9% sequence identity to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively. In some embodiments, the first and second nucleotide sequences are identical to CS04-HC-NA and CS04-LC-NA (SEQ ID NOS 3 and 4), respectively.

[0317] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS04-SC1-NA (SEQ ID NO: 9). In some embodiments, the nucleotide sequence has at least 95% identity to CS04-SC1-NA (SEQ ID NO: 9). In some embodiments, the nucleotide sequence has at least 96% identity to CS04-SC1-NA (SEQ ID NO: 9). In some embodiments, the nucleotide sequence has at least 97% identity to CS04-SC1-NA (SEQ ID NO: 9). In some embodiments, the nucleotide sequence

has at least 98% identity to CS04-SC1-NA (SEQ ID NO: 9). In some embodiments, the nucleotide sequence has at least 99% identity to CS04-SC1-NA (SEQ ID NO: 9). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS04-SC1-NA (SEQ ID NO: 9). In some embodiments, the nucleotide sequence has at least 99.9% identity to CS04-SC1-NA (SEQ ID NO: 9). In some embodiments, the nucleotide sequence is identical to CS04-SC1-NA (SEQ ID NO: 9).

[0318] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS04-SC2-NA (SEQ ID NO: 11). In some embodiments, the nucleotide sequence has at least 95% identity to CS04-SC2-NA (SEQ ID NO: 11). In some embodiments, the nucleotide sequence has at least 96% identity to CS04-SC2-NA (SEQ ID NO: 11). In some embodiments, the nucleotide sequence has at least 97% identity to CS04-SC2-NA (SEQ ID NO: 11). In some embodiments, the nucleotide sequence has at least 98% identity to CS04-SC2-NA (SEQ ID NO: 11). In some embodiments, the nucleotide sequence has at least 99% identity to CS04-SC2-NA (SEQ ID NO: 11). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS04-SC2-NA (SEQ ID NO: 11). In some embodiments, the nucleotide sequence has at least 99.9% identity to CS04-SC2-NA (SEQ ID NO: 11). In some embodiments, the nucleotide sequence is identical to CS04-SC2-NA (SEQ ID NO: 11).

[0319] In some embodiments, the single-chain Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS04-SC1-AA (SEQ ID NO: 10; human Factor VIIIΔ(760-1667) (SPI; HsFVIIIΔ(741-1648), SPE)). In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS04-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 97% identity to CS04-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 98% identity to CS04-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99% identity to CS04-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99.5% identity to CS04-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99.9% identity to CS04-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence is identical to CS04-SC1-AA (SEQ ID NO: 10).

[0320] In some embodiments, the Factor VIII variant encoded by the CS04-SC1 polynucleotide, having high sequence homology to CS04-SC1-AA (e.g., at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0321] In some embodiments, the single-chain Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS04-SC2-AA (SEQ ID NO: 12; human Factor VIIIΔ(772-1667) (SPI; HsFVIIIΔ(753-1648), SPE)). In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS04-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 97% identity to CS04-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 98% identity to CS04-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99% identity to CS04-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99.5% identity to CS04-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99.9% identity to CS04-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence is identical to CS04-SC2-AA (SEQ ID NO: 12).

[0322] In some embodiments, the single-chain Factor VIII variant encoded by the CS04-SC2 polynucleotide, having high sequence homology to CS04-SC2-AA (e.g., at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0323] In one embodiment, the single-chain Factor VIII variant encoded by the CS04 polynucleotide comprises an m1 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m2 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m3 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m4 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises an m5 amino acid substitution.

[0324] In one embodiment, the single-chain Factor VIII variant encoded by the CS04 polynucleotide comprises m12 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m13 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m23 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m24 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m25 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m34 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m35 amino acid substitutions.

[0325] In one embodiment, the single-chain Factor VIII variant encoded by the CS04 polynucleotide comprises m123 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m234 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS04 polynucleotide comprises m125 amino acid substitutions.

[0326] Single-Chain CS01 Codon Altered Polynucleotides

[0327] In one embodiment, the codon-altered polynucleotides provided herein include a nucleotide sequence encoding a single-chain Factor VIII variant polypeptide. The Factor VIII polypeptide includes a Factor VIII light chain, a Factor VIII heavy chain, and an optional polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having high sequence identity to CS01-HC-NA (SEQ ID NO: 24), which is the portion of CS01-FL-NA (SEQ ID NO: 13) encoding for a Factor VIII heavy chain. The light chain of the Factor VIII polypeptide is encoded by a second nucleotide sequence with high sequence identity to CS01-LC-NA

(SEQ ID NO: 25), which is the portion of CS01-FL-NA (SEQ ID NO: 13) encoding for a Factor VIII light chain. The optional polypeptide linker does not include a furin cleavage site.

[0328] In some embodiments, the first and second nucleotide sequences have at least 95% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 96% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 97% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 98% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 99% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.5% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.9% sequence identity to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively. In some embodiments, the first and second nucleotide sequences are identical to CS01-HC-NA and CS01-LC-NA (SEQ ID NOS 24 and 25), respectively.

[0329] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS01-SC1-NA (SEQ ID NO: 26). In some embodiments, the nucleotide sequence has at least 95% identity to CS01-SC1-NA (SEQ ID NO: 26). In some embodiments, the nucleotide sequence has at least 96% identity to CS01-SC1-NA (SEQ ID NO: 26). In some embodiments, the nucleotide sequence has at least 97% identity to CS01-SC1-NA (SEQ ID NO: 26). In some embodiments, the nucleotide sequence has at least 98% identity to CS01-SC1-NA (SEQ ID NO: 26). In some embodiments, the nucleotide sequence has at least 99% identity to CS01-SC1-NA (SEQ ID NO: 26). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS01-SC1-NA (SEQ ID NO: 26). In some embodiments, the nucleotide sequence has at least 99.9% identity to CS01-SC1-NA (SEQ ID NO: 26). In some embodiments, the nucleotide sequence is identical to CS01-SC1-NA (SEQ ID NO: 26).

[0330] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS01-SC2-NA (SEQ ID NO: 27). In some embodiments, the nucleotide sequence has at least 95% identity to CS01-SC2-NA (SEQ ID NO: 27). In some embodiments, the nucleotide sequence has at least 96% identity to CS01-SC2-NA (SEQ ID NO: 27). In some embodiments, the nucleotide sequence has at least 97% identity to CS01-SC2-NA (SEQ ID NO: 27). In some embodiments, the nucleotide sequence has at least 98% identity to CS01-SC2-NA (SEQ ID NO: 27). In some embodiments, the nucleotide sequence has at least 99% identity to CS01-SC2-NA (SEQ ID NO: 27). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS01-SC2-NA (SEQ ID NO: 27). In some embodiments, the nucleotide sequence has at least 99.9% identity to CS01-SC2-NA (SEQ ID NO: 27). In some embodiments, the nucleotide sequence is identical to CS01-SC2-NA (SEQ ID NO: 27).

[0331] In some embodiments, the single-chain Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS01-SC1-AA (SEQ ID NO: 10; human Factor VIIIΔ(760-1667) (SPI; HsFVIIIΔ(741-1648), SPE)). In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS01-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 97% identity to CS01-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 98% identity to CS01-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99% identity to CS01-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99.5% identity to CS01-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99.9% identity to CS01-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence is identical to CS01-SC1-AA (SEQ ID NO: 10).

[0332] In some embodiments, the Factor VIII variant encoded by the CS01-SC1 polynucleotide, having high sequence homology to CS01-SC1-AA (e.g., at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0333] In some embodiments, the single-chain Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS01-SC2-AA (SEQ ID NO: 12; human Factor VIIIΔ(772-1667) (SPI; HsFVIIIΔ(753-1648), SPE)). In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS01-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 97% identity to CS01-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 98% identity to CS01-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99% identity to CS01-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99.5% identity to CS01-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99.9% identity to CS01-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence is identical to CS01-SC2-AA (SEQ ID NO: 12).

[0334] In some embodiments, the single-chain Factor VIII variant encoded by the CS01-SC2 polynucleotide, having high sequence homology to CS01-SC2-AA (e.g., at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0335] In one embodiment, the single-chain Factor VIII variant encoded by the CS01 polynucleotide comprises an m1 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m2 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m3 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m4 amino acid substitution. In one

embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises an m5 amino acid substitution.

[0336] In one embodiment, the single-chain Factor VIII variant encoded by the CS01 polynucleotide comprises m12 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m13 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m23 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m24 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m25 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m34 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m35 amino acid substitutions.

[0337] In one embodiment, the single-chain Factor VIII variant encoded by the CS01 polynucleotide comprises m123 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m234 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS01 polynucleotide comprises m125 amino acid substitutions.

[0338] Single-Chain CS23 Codon Altered Polynucleotides

[0339] In one embodiment, the codon-altered polynucleotides provided herein include a nucleotide sequence encoding a single-chain Factor VIII variant polypeptide. The Factor VIII polypeptide includes a Factor VIII light chain, a Factor VIII heavy chain, and an optional polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain. The heavy chain of the Factor VIII polypeptide is encoded by a first nucleotide sequence having high sequence identity to CS23-HC-NA (SEQ ID NO: 22), which is the portion of CS23-FL-NA (SEQ ID NO: 20) encoding for a Factor VIII heavy chain. The light chain of the Factor VIII polypeptide is encoded by a second nucleotide sequence with high sequence identity to CS23-LC-NA (SEQ ID NO: 23), which is the portion of CS23-FL-NA (SEQ ID NO: 20) encoding for a Factor VIII light chain. The optional polypeptide linker does not include a furin cleavage site.

[0340] In some embodiments, the first and second nucleotide sequences have at least 95% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 96% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 97% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 98% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 99% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.5% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences have at least 99.9% sequence identity to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively. In some embodiments, the first and second nucleotide sequences are identical to CS23-HC-NA and CS23-LC-NA (SEQ ID NOS 22 and 23), respectively.

[0341] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS23-SC1-NA (SEQ ID NO: 28). In some embodiments, the nucleotide sequence has at least 95% identity to CS23-SC1-NA (SEQ ID NO: 28). In some embodiments, the nucleotide sequence has at least 96% identity to CS23-SC1-NA (SEQ ID NO: 28). In some embodiments, the nucleotide sequence has at least 97% identity to CS23-SC1-NA (SEQ ID NO: 28). In some embodiments, the nucleotide sequence has at least 98% identity to CS23-SC1-NA (SEQ ID NO: 28). In some embodiments, the nucleotide sequence has at least 99% identity to CS23-SC1-NA (SEQ ID NO: 28). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS23-SC1-NA (SEQ ID NO: 28). In some embodiments, the nucleotide sequence has at least 99.9% identity to CS23-SC1-NA (SEQ ID NO: 28). In some embodiments, the nucleotide sequence is identical to CS23-SC1-NA (SEQ ID NO: 28).

[0342] In some embodiments, the codon-altered polynucleotide has a nucleotide sequence with high sequence identity to CS23-SC2-NA (SEQ ID NO: 29). In some embodiments, the nucleotide sequence has at least 95% identity to CS23-SC2-NA (SEQ ID NO: 29). In some embodiments, the nucleotide sequence has at least 96% identity to CS23-SC2-NA (SEQ ID NO: 29). In some embodiments, the nucleotide sequence has at least 97% identity to CS23-SC2-NA (SEQ ID NO: 29). In some embodiments, the nucleotide sequence has at least 98% identity to CS23-SC2-NA (SEQ ID NO: 29). In some embodiments, the nucleotide sequence has at least 99% identity to CS23-SC2-NA (SEQ ID NO: 29). In some embodiments, the nucleotide sequence has at least 99.5% identity to CS23-SC2-NA (SEQ ID NO: 29). In some embodiments, the nucleotide sequence has at least 99.9% identity to CS23-SC2-NA (SEQ ID NO: 29). In some embodiments, the nucleotide sequence is identical to CS23-SC2-NA (SEQ ID NO: 29).

[0343] In some embodiments, the single-chain Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS23-SC1-AA (SEQ ID NO: 10; human Factor VIIIΔ(760-1667) (SPI; CS04Δ(741-1648), SPE)). In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS23-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 97% identity to CS23-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 98% identity to CS23-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99% identity to CS23-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99.5% identity to CS23-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence has at least 99.9% identity to CS23-SC1-AA (SEQ ID NO: 10). In some embodiments, the amino acid sequence is identical to CS23-SC1-AA (SEQ ID NO: 10).

[0344] In some embodiments, the Factor VIII variant encoded by the CS23-SC1 polynucleotide, having high sequence homology to CS23-SC1-AA (e.g., at least 95%,

96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0345] In some embodiments, the single-chain Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS23-SC2-AA (SEQ ID NO: 12; human Factor VIIIΔ(772-1667) (SPI; HsFVIIIΔ(753-1648), SPE)). In some embodiments, the Factor VIII variant encoded by the codon-altered polynucleotide has an amino acid sequence with high sequence identity to CS23-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 97% identity to CS23-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 98% identity to CS23-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99% identity to CS23-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99.5% identity to CS23-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence has at least 99.9% identity to CS23-SC2-AA (SEQ ID NO: 12). In some embodiments, the amino acid sequence is identical to CS23-SC2-AA (SEQ ID NO: 12).

[0346] In some embodiments, the single-chain Factor VIII variant encoded by the CS23-SC2 polynucleotide, having high sequence homology to CS23-SC2-AA (e.g., at least 95%, 96%, 97%, 98%, 99%, 99.5%, or 99.9% identity), comprises one or more amino acid substitutions selected from m1, m2, m3, m4, and m5.

[0347] In one embodiment, the single-chain Factor VIII variant encoded by the CS23 polynucleotide comprises an m1 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m2 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m3 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m4 amino acid substitution. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises an m5 amino acid substitution.

[0348] In one embodiment, the single-chain Factor VIII variant encoded by the CS23 polynucleotide comprises m12 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m13 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m23 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m24 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m25 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m34 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m35 amino acid substitutions.

[0349] In one embodiment, the single-chain Factor VIII variant encoded by the CS23 polynucleotide comprises m123 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m234 amino acid substitutions. In one embodiment, the Factor VIII variant encoded by the CS23 polynucleotide comprises m125 amino acid substitutions.

[0350] E. Factor VIII Expression Vectors

[0351] In some embodiments, the codon-altered polynucleotides described herein are integrated into expression vectors. Non-limiting examples of expression vectors include viral vectors (e.g., vectors suitable for gene therapy), plasmid vectors, bacteriophage vectors, cosmids, phagemids, artificial chromosomes, and the like.

[0352] Non-limiting examples of viral vectors include: retrovirus, e.g., Moloney murine leukemia virus (MMLV), Harvey murine sarcoma virus, murine mammary tumor virus, and Rous sarcoma virus; adenoviruses, adeno-associated viruses; SV40-type viruses; polyomaviruses; Epstein-Barr viruses; papilloma viruses; herpes viruses; vaccinia viruses; and polio viruses.

[0353] In some embodiments, the codon-altered polynucleotides described herein are integrated into a gene therapy vector. In some embodiments, the gene therapy vector is a retrovirus, and particularly a replication-deficient retrovirus. Protocols for the production of replication-deficient retroviruses are known in the art. For review, see Kriegler, M., Gene Transfer and Expression, A Laboratory Manual, W.H. Freeman Co., New York (1990) and Murry, E. J., Methods in Molecular Biology, Vol. 7, Humana Press, Inc., Cliffton, N.J. (1991).

[0354] In one embodiment, the gene therapy vector is an adeno-associated virus (AAV) based gene therapy vector. AAV systems have been described previously and are generally well known in the art (Kelleher and Vos, *Biotechniques,* 17(6):1110-17 (1994); Cotten et al., *Proc Natl Acad Sci USA,* 89(13):6094-98 (1992); Curiel, *Nat Immun,* 13(2-3):141-64 (1994); Muzyczka, *Curr Top Microbiol Immunol,* 158:97-129 (1992); and Asokan A, et al., Mol. Ther., 20(4): 699-708 (2012), each incorporated herein by reference in their entireties for all purposes). Details concerning the generation and use of rAAV vectors are described, for example, in U.S. Pat. Nos. 5,139,941 and 4,797,368, each incorporated herein by reference in their entireties for all purposes. In a particular embodiment, the AAV vector is an AAV-8 vector.

[0355] In some embodiments, the codon-altered polynucleotides described herein are integrated into a retroviral expression vector. These systems have been described previously, and are generally well known in the art (Mann et al., *Cell,* 33:153-159, 1983; Nicolas and Rubinstein, In: Vectors: A survey of molecular cloning vectors and their uses, Rodriguez and Denhardt, eds., Stoneham: Butterworth, pp. 494-513, 1988; Temin, In: Gene Transfer, Kucherlapati (ed.), New York: Plenum Press, pp. 149-188, 1986). In a specific embodiment, the retroviral vector is a lentiviral vector (see, for example, Naldini et al., *Science,* 272(5259): 263-267, 1996; Zufferey et al., *Nat Biotechnol,* 15(9):871-875, 1997; Blomer et al., *J Virol.,* 71(9):6641-6649, 1997; U.S. Pat. Nos. 6,013,516 and 5,994,136).

[0356] A wide variety of vectors can be used for the expression of a Factor VIII polypeptide from a codon-altered polypeptide in cell culture, including eukaryotic and prokaryotic expression vectors. In certain embodiments, a plasmid vector is contemplated for use in expressing a Factor VIII polypeptide in cell culture. In general, plasmid vectors containing replicon and control sequences which are derived from species compatible with the host cell are used in connection with these hosts. The vector can carry a replication site, as well as marking sequences which are capable of providing phenotypic selection in transformed cells. The plasmid will include the codon-altered polynucle-

otide encoding the Factor VIII polypeptide, operably linked to one or more control sequences, for example, a promoter.

[0357] Non-limiting examples of vectors for prokaryotic expression include plasmids such as pRSET, pET, pBAD, etc., wherein the promoters used in prokaryotic expression vectors include lac, trc, trp, recA, araBAD, etc. Examples of vectors for eukaryotic expression include: (i) for expression in yeast, vectors such as pAO, pPIC, pYES, pMET, using promoters such as AOX1, GAP, GAL1, AUG1, etc; (ii) for expression in insect cells, vectors such as pMT, pAc5, pIB, pMIB, pBAC, etc., using promoters such as PH, p10, MT, Ac5, OpIE2, gp64, polh, etc., and (iii) for expression in mammalian cells, vectors such as pSVL, pCMV, pRc/RSV, pcDNA3, pBPV, etc., and vectors derived from viral systems such as vaccinia virus, adeno-associated viruses, herpes viruses, retroviruses, etc., using promoters such as CMV, SV40, EF-1, UbC, RSV, ADV, BPV, and β-actin.

IV. Examples

Example 1—Construction of a Codon Altered Factor VIII Variant Expression Sequence

[0358] Two hurdles had to be overcome in order to create a Factor VIII coding sequence that is effective for gene therapy of hemophilia A. First, because of the genomic size limitations of conventional gene therapy delivery vectors (e.g., AAV virions), the encoded Factor VIII polypeptide had to be shortened considerably. Second, the coding sequence had to be altered to: (i) stabilize packaging interactions within the delivery vector, (ii) stabilize the mRNA intermediary, and (iii) improve the robustness of transcription/translation of the mRNA.

[0359] To achieve the first objective, Applicants started with a B-domain deleted Factor VIII variant construct, referred to herein as "FVIII-BDD-SQ." In this construct, the B-domain is replaced with a fourteen amino acid sequence referred to as the "SQ" sequence. Recombinant FVIII-BDD-SQ is sold under the trade name REFACTO®, and has been shown to be effective for the management of hemophilia A. However, the native coding sequence for FVIII-BDD-SQ, which includes human wild-type nucleic acid sequences for the Factor VIII heavy and light chains, is ineffectively expressed in gene therapy vectors.

[0360] To address the poor expression of the native FVIII-BDD-SQ, the codon optimization algorithm described in Fath et al. (PLoS ONE, 6:e17596 (2011)), modified as described in Ward et al. (Blood, 117:798 (2011)) and in McIntosh et al. (Blood, 121, 3335-3344 (2013)), was applied to the FVIII-BDD-SQ sequence to create first intermediate coding sequence CS04a. However, Applicants recognized that the CS04a sequence created using the modified algorithm could be improved by further modifying the sequence. Accordingly, Applicants re-introduced CpG dinucleotides, re-introduced the CGC codon for arginine, changed the leucine and serine codon distributions, re-introduced highly conserved codon pairs, and removed cryptic TATA box, CCAAT box, and splice site elements, while avoiding CpG islands and local overrepresentation of AT-rich and GC-rich stretches.

[0361] First, the modified algorithm systematically replaces codons containing CpG-dinucleotides (e.g., arginine codons) with non-CpG-dinucleotide codons, and eliminates/avoids CpG-dinucleotides created by neighboring codons. This strict avoidance of CpG dinucleotides is usually done to prevent TLR-induced immunity after intramuscular injection of DNA vaccines. However, doing so limits the codon optimization possibilities. For example, the modified algorithm excludes use of the complete set of CGX arginine codons. This is particularly disruptive in the coding of genes for expression in human cells, because CGC is the most frequently used arginine codon in highly expressed human genes. Additionally, avoiding the creation of CpGs by neighboring codons further limits the optimization possibilities (e.g., limits the number of codon pairs that may be used together).

[0362] Because TLR-induced immunity is not expected to be a problem associated with liver-directed, AAV-based gene therapy, codons including CpGs, and neighboring codons creating CpGs, were re-introduced into intermediate coding sequence CS04a, preferentially in the sequence coding for the Factor VIII light chain (e.g., at the 3' end of the FVIII-BDD-SQ coding sequence). This allowed for more frequent use of preferred human codons, particularly those for arginine. Care was taken, however, to avoid creation of CpG islands, which are regions of coding sequence having a high frequency of CpG sites. This is contrary to the teachings of Krinner et al. (Nucleic Acids Res., 42(6):3551-64 (2014)), which suggests that CpG domains downstream of transcriptional start sites promote high levels of gene expression.

[0363] Second, the modified algorithm applies certain codons exclusively, such as CTG for leucine, GTG for valine, and CAG for glutamine. However, this offends the principles of balanced codon use, for example, as proposed in Haas et al. (Current Biology, 6(3):315-24 (1996)). To account for the overuse of preferred codons by the modified algorithm, alternate leucine codons were re-introduced where allowed by the other rules applied to the codon alteration (e.g., CpG frequency and GC content).

[0364] Third, the modified algorithm replaces codon pairs without regard to how conserved they are in nature, when certain criteria (e.g., the presence of CG-dinucleotides) are met. To account for beneficial properties which may have been conserved by evolution, the most conserved codon pairs that were replaced by the algorithm and the most conserved preferred codon pairs, e.g., as described in Tats et al. (BMC Genomics 9:463 (2008)), were analyzed and adjusted where allowed by the other rules applied to the codon alteration (e.g., CpG frequency and GC content).

[0365] Fourth, serine codons used in the intermediate coding sequence were also re-engineered. Specifically, AGC, TCC, and TCT serine codons were introduced into the modified coding sequence with higher frequency, to better match overall for human codon usage (Haas et al., supra).

[0366] Fifth, TATA box, CCAAT box elements, and intron/exon splice sites were screened and removed from the modified coding sequence. When modifying the coding sequence, care was taken to avoid local overrepresentation of AT-rich or GC rich stretches.

[0367] Finally, in addition to optimizing the codon usage within the coding sequence, the structural requirements of the underlying AAV virion were considered when further refining the intermediate coding sequence CS04a. AAV vectors (e.g., the nucleic acid portion of an AAV virion) are packaged as single stranded DNA molecules into their capsids (for review, see, Daya and Berns, Clin. Microbiol Rev., 21(4):583-93 (2008)). The GC content of the vector is therefore likely to influence packaging of the genome and,

thus, vector yields during production. Like many algorithms, the modified algorithm used here creates an optimized gene sequence with a GC content of at least 60% (see, Fath et al., PLoS One, 6(3):e17596 (2011) (erratum in: PLoS One, (6)3 (2011)). However, the AAV8 capsid protein is encoded by a nucleotide sequence having a lower GC content of about 56%. Thus, to better mimic the native AAV8 capsid protein coding sequence, the GC content of the intermediate coding sequence CS04a was reduced to 56%.

[0368] The resulting CS04 coding sequence, shown in FIG. **2**, has an overall GC content of 56%. The CpG-dinucleotide content of the sequence is moderate. However, CpG dinucleotides are predominantly present in the downstream portion of the coding sequence, e.g., the portion coding for the Factor VIII light chain. The CS04 sequence has 79.77% nucleotide sequence identity to the corresponding coding sequences in wild-type Factor VIII (Genbank accession M14113).

[0369] For comparison purposes, several other codon-optimized, ReFacto constructs were prepared. CS01 was constructed by applying the codon-optimization algorithm of Fath et al., as modified by Ward et al., as done for CS04. However, unlike CS04, the CS01 construct does not contain any CpG islands. The CS08 ReFacto construct was codon-optimized as described in Radcliff P. M. et al., Gene Therapy, 15:289-97 (2008), the content of which is hereby expressly incorporated by reference herein, in its entirety, for all purposes. The CS10 codon-optimized ReFacto construct was obtained from Eurofins Genomics (Ebersberg, Germany). The CS11 codon-optimized ReFacto construct was obtained from Integrated DNA Technologies, Inc. (Coralville, USA). The CH25 codon-optimized ReFacto construct was obtained from ThermoFischer Scientific's GeneArt services (Regensburg, Germany). The CS40 ReFacto construct consists of the wild type Factor VIII coding sequence. The algorithm used to construct CS23 is based on the JCAT tool (www.jcat.de), an on-line tool for codon-optimizations (Grote et al., 2005; Nucl. Acids Res. W526-31). The sequence was further modified to more reflect the codon usage of the albumin superfamily (Mirsafian et al. 2014: Sc. Word Journal 2014, ID 639682). The sequence identities shared between each of the ReFacto coding sequences is shown in Table 2, below.

TABLE 2

Percent identity matrix for codon-altered Factor VIII constructs.

	CS01	CS04	CS08	CS10	CS11	CS40	CH25	CS23
CS01	100%							
CS04	93.0%	100%						
CS08	80.7%	82.2.%	100%					
CS10	79.1%	79.4%	78.4%	100%				
CS11	78.3%	78.3%	78.1%	77.5%	100%			
CS40	79.6%	79.8%	76.7%	77.6%	75.4%	100%		
CH25	81.3%	85.1%	85.0%	79.9%	79.4%	75.8%	100%	
CS23	84.3%	89.2%	85.1%	80.3%	79.9	76.5%	93.2%	100%

[0370] Plasmids of each construct were constructed by cloning different synthetic DNA fragments into the same vector backbone plasmid (pCh-BB01). DNA synthesis of the Refacto-type BDD-FVIII fragments with flanking AscI and NotI enzyme restriction sites were done by ThermoFischer Scientific (Regensburg, Germany). The vector backbone contains two flanking AAV2-derived inverted terminal repeats (ITRs) that encompass a promoter/enhancer sequence derived from the liver-specific murine transthyretin gene, AscI and NotI enzyme restriction sites for insertion of the respective Refacto-type BDD-FVIII and a synthetic polyA site. After ligation of the prepared vector backbone and inserts via the AscI and NotI sites, the resulting plasmids were amplified in milligram scale. The Refacto-type BDD-FVIII sequences of the constructs were verified by direct sequencing (Microsynth, Balgach, Switzerland). The cloning resulted in seven different plasmid constructs named pCS40, pCS01, pCS04, pCS08, pCS10, pCS11, and pCh25 (FIG. **23**). The constructs have the same vector backbone and encode the same B-domain deleted FVIII protein (Refacto-type BDD-FVIII), but differ in their FVIII coding sequence.

[0371] AAV8-based vectors were prepared by the three plasmid transfection method, as described in Grieger J C, et al. (Virus Vectors Using Suspension HEK293 Cells and Continuous Harvest of Vector From the Culture Media for GMP FIX and FLT1 Clinical Vector, Mol Ther., October 6. (2015) doi: 10.1038/mt.2015.187. [Epub ahead of print]), the content of which is hereby expressly incorporated by reference herein, in its entirety, for all purposes. HEK293 suspensions cells were used for plasmid transfections using the corresponding FVIII vector plasmid, the helper plasmid pXX6-80 (carrying adenoviral helper genes), and the packaging plasmid pGSK2/8 (contributing the rep2 and cap8 genes). To isolate the AAV8 constructs, the cell pellets of one liter cultures were processed using iodixanol gradients, as described in Grieger et al. (2015, Supra). The procedure resulted in vector preparations called vCS01, vCS04, vCS08, vCS10, vCS11, and vCH25. Vectors were quantified by qPCR using the universal qPCR procedure targeting the AAV2 inverted terminal repeats (Aurnhammer, Human Gene Therapy Methods: Part B 23:18-28 (2012)). A control vector plasmid carrying AAV2 inverted terminal repeats served for preparing the standard curve. The resulting vCS04 construct is presented as SEQ ID NO: 8 in FIGS. **7A-7C**.

[0372] The integrity of the vector genomes was analyzed by AAV agarose gel electrophoresis. The electrophoresis was performed as described in Fagone et al., Human Gene Therapy Methods 23:1-7 (2012). Briefly, AAV vector preparations were incubated at 75° C. for 10 minutes in the presence of 0.5% SDS and then cooled down to room temperature. Approximately 1.5E10 vector genomes (vg) were loaded per lane on a 1% 1×TAE agarose gel and electrophoresed for 60 min at 7 V/cm of gel length. The gel was then stained in 2× GelRed (Biotium Cat#41003) solution and imaged by ChemiDocTMMP (Biorad). The results

shown in FIG. **24** demonstrate that the vCS01, vCS04, and vCS40 viral vectors have the same-sized genome, indicated by a distinct band in the 5 kb range (FIG. **24**, lanes 2-4). Despite a vector size of approx. 5.2 kb, the genome is a homogenous band confirming correct packaging of the somewhat oversized genome (relative to an AAV wild-type genome of 4.7 kb). All other vCS vector preparations show the same genomic size (data not shown).

[0373] In order to confirm the expected pattern of capsid proteins, SDS PAGE followed by silver staining was performed with the vectors vCS01, vCS04, and vCS40 (FIG. **25**). As shown in the figure, the downstream purification procedure resulted in highly purified material displaying the expected protein pattern of VP1, VP2 and VP3 (FIG. **25**, lanes 2-4). The same pattern was seen with all other viral preparations (not shown). The SDS-PAGE procedure of AAV preparations was done according to standard procedures. Each lane contained 1E10 vg of the respective viral construct, and were separated on a 4-12% Bis-Tris (NuPAGE® Novex, Life Technologies) gel as per manufacturer's instructions. Silver staining was performed with a SilverQuest™ kit (Novex, Life Technologies) according to the manufacturer's instructions.

[0374] Surprisingly, AAV vectors vCS01 and vCS04 had higher virion packaging, measured by higher yields in AAV virus production, as compared to the vCS40 wild-type coding construct and the other codon-optimized constructs. As shown in Table 3, the vCS01 and vCS04 vectors replicated substantially better than vCS40, providing a 5-7 fold yield increase in AAV titer.

TABLE 3

Yields per liter cell culture obtained with AAV vector constructs vCS01, vCS04, and vCD40, as purified from cell pellets.

Construct	Vector concentration [vg/ml] × 10E12	Yields [vg/liter] × 10E12	Fold increase vs wt
vCS40	2.0	11.0	—
vCS01	9.2	51.4	4.7
vCS04 - Sample 1	17.6	79.2	7.2
vCS04 - Sample 2	15.9	58.8	5.4

Example 2—In Vivo Expression of Codon Altered Factor VIII Variant Expression Sequences

[0375] To test the biological potency of the codon-altered Factor VIII variant sequences, the ReFacto-type FVIII constructs described in Example 1 were administered to mice lacking Factor VIII. Briefly, the assays were performed in C57Bl/6 FVIII knock-out (ko) mice (with 6-8 animals per group) by tail vein injection of 4E12 vector genomes (vg) per kilogram body weight of mouse. Blood was drawn 14 days after injection by retroorbital puncture and plasma was prepared and frozen using standard procedures. Expression levels at day 14 were chosen because there is minimal influence of inhibitory antibodies at this time, which are seen in some animals of this mouse model at later times. FVIII activity in the mouse plasma was determined using the Technochrome FVIII assay performed, with only minor modifications, as suggested by the manufacture (Technoclone, Vienna, Austria). For the assay, the plasma samples were appropriately diluted and mixed with assay reagents, containing thrombin, activated factor IX (FIXa), phospholipids, factor X and calcium. Following FVIII activation by thrombin a complex with FIXa, phospholipids and calcium is formed. This complex activates FX to activated FX (FXa) which in turn cleaves para-nitroanilide (pNA) from the chromogenic substrate. The kinetics of pNA formation is measured at 405 nm. The rate is directly proportional to the FVIII concentration in the sample. FVIII concentrations are read from a reference curve and results are given in IU FVIII/milliliter.

[0376] The results, presented in Table 4 below, demonstrate that the codon-altered sequences designed using commercial algorithms (CS10, CS11, and CH25) provided only a modest increase in BDD-Factor VIII (3-4 fold) as compared to the wild-type BDD-Factor VIII construct (CS40). Similarly, the codon-altered BDD-Factor VIII construct prepared as described in Radcliffe et al. (CS08), only provided a 3-4 fold increase in BDD-FVIII expression. This result is consistent with the results reported in Radcliff et al. Surprisingly, the CS01, CS04, and CS23 constructs provided much higher BDD-FVIII expression in the in-vivo biopotency assays (18-, 74-, and -30-fold increases, respectively).

TABLE 4

Expression of FVIII in the plasma of FVIII-knock-out mice induced by the different AAV vector constructs.

Construct	Codon Algorithm	Average FVIII Expression at Day 14 [IU/ml]	Standard deviation	Number of mice	Fold increase vs wt
vCS40	Human wild-type	0.03	0.03	12	—
vCS01	Applicants'	0.55	0.28	22	18.3
vCS04	Applicants'	2.21	1.20	55	73.7
vCS08	Radcliffe et al.	0.11	0.01	6	3.6
vCS10	Eurofins	0.09	0.01	7	3.0
vCS11	IDT	0.08	0.02	8	2.7
vCH25	GeneArt	0.13	0.12	18	4.3
vCS23	Applicants'	0.91	0.32	5	30.3

Example 3—Design of Glycosylation Peptides for the B-Domain Substituted Linker

[0377] Others have shown that inclusion of a small peptide (the "V3 peptide") containing six putative N-linked glycosylation sites from the wild-type Factor VIII B-domain, into a B-domain deleted gene therapy construct, increased Factor VIII levels in the plasma of mice (McIntosh et al., Blood 121(17):3335-44 (2013)). However, in order to maintain the small size of the B-domain substituted linker, the glycosylation sites were taken out of the context of the wild-type B-domain. In silico prediction (Gupta et al., Supra) of the linker containing the V3 peptide suggests that only two of these glycosylation sites in the V3 peptide will be modified in vivo (FIG. **15**).

[0378] Thus, Applicants attempted to identify alternative glycosylation peptides that would support higher levels of glycosylation in vivo, which matched wild type glycosylation more closely than the V3 peptide. Applicants designed and tested several alternative glycosylation peptides, in silico. Several of these peptides, shown in FIGS. **13A-13B**, were predicted to have equal or greater glycosylation in vivo than the V3 peptide, when placed between amino acids N768 and P769 of the B-domain substituted linker in SEQ

ID NO:2. The results of the in silico predictions are shown in Table 5, below. Table 5 also reports the results of expression experiments performed for several constructs encoding a ReFacto-type Factor VIII protein with a glycosylation peptide incorporated into the B-domain substituted linker, in a CS01 codon-optimized background.

TABLE 5

Prediction of N-glycosylation in B-domain substituted linker peptides and performance of AAV vector constructs in vivo.

Sequence	Number of Predicted N-glycosylation sites	Day 28 expression [IU/ml]	SD	Number of mice [n]	Fold expression
vCS01	0	0.74	0.52	5	21
vNG1/CS01	4	n.d.	—	—	—
vNG4/CS01	3	1.93	0.57	6	55
vNG5/CS01	2	n.d.	—	—	—
vNG6/CS01	1	0.80	0.67	5	23
vNG9/CS01	1	n.d.	—	—	—
vNG10/CS01	2	2.66	0.52	6	76
vNG16/CS01	2	1.59	0.57	6	45
vNG17/CS01	2	n.d.	—	—	—
vNG18/CS01	2	n.d.	—	—	—
vNG19/CS01	2	0.88	0.25	5	25
vNG20/CS01	2	n.d.	—	—	—
vNG21/CS01	2	n.d.	—	—	—
vCS40	0	0.035	0.030	12	1

[0379] AAV vectors containing the NG variants were constructed as described in Example 1 and tested in FVIII knock-out mice as described in Example 2. All virus vectors (except the control vector vCS40) shown in Table 5 are based on the algorithm as used in vCS01. A parallel set of constructs using the algorithm of vCS04 was also prepared (vNG/CS04 series) and is tested in the mouse model. Results were compared to the expression levels achieved with the wild-type vCS40 construct. The day 28 expression levels were chosen in this example, because expression levels of the majority of construct reached the highest levels at this time point. Three AAV vectors achieved greater than 40-fold FVIII expression levels including vNG4/CS01, vNG10/CS01 and vNG16/CS01 (Table 5). The corresponding constructs vNG4/CS04, vNG10/CS04 and vNG16/CS04 are expected to show even higher expression because they are based on the superior vCS04 algorithm.

[0380] Surprisingly, the AAV vectors of the vNG/CS01 series had higher virion packaging, measured by higher yields in AAV virus production, as compared to the vCS40 wild-type coding construct. As shown in Table 6, the vNG/CS01-based vectors replicated substantially better than vCS40, providing an approximately 3-fold yield increase in AAV titer.

TABLE 6

Yields per liter cell culture obtained with AAV vector constructs as purified from cell pellets.

Sequence	Vector conc. [vg/ml] × 10^{12}	Yields [vg/liter] × 10^{12}	Fold increase vs wild-type
vCS01	9.17	51.35	4.7
vNG1/CS01	2.13	17.04	1.5
vNG4/CS01	5.74	33.01	3.0
vNG5/CS01	6.91	27.29	2.5

TABLE 6-continued

Yields per liter cell culture obtained with AAV vector constructs as purified from cell pellets.

Sequence	Vector conc. [vg/ml] × 10^{12}	Yields [vg/liter] × 10^{12}	Fold increase vs wild-type
vNG6/CS01	7.01	40.66	3.7
vNG9/CS01	6.39	29.39	2.7
vNG10/CS01	8.57	37.71	3.4
vNG16/CS01	5.3	28.36	2.6
vNG17/CS01	4.24	32.22	2.9
vNG18/CS01	6.11	37.88	3.4
vNG19/CS01	9.42	39.56	3.6
vNG20/CS01	4.09	30.27	2.8
vNG21/CS01	n.d	—	—
vCS40	2.03	11	1.0

Example 4—Construction of Mutant BDD-FVIII Constructs

[0381] Numerous different mutated Refacto-type BDD-FVIII constructs, carrying amino acid mutations within the Factor VIII heavy chain and/or B-domain substituted linker, were cloned and screened. The corresponding vectors, as referred to herein as the "vCS" series of vectors, encode BDD-FVIII variants in the CS01, CS04, and CS23 codon-altered backgrounds. The method used to construct the CS01 and CS04 backgrounds is described in Example 1. The method used to construct CS23 was based on the JCAT tool (www.jcat.de), an on-line tool for codon-optimizations (Grote et al., 2005; Nucl. Acids Res. W526-31). The sequence was further modified to better reflect the codon usage of the albumin superfamily (Mirsafian et al., Sc. Word Journal, ID 639682 (2014)), the content of which is hereby expressly incorporated by reference, in its entirety, for all purposes.

[0382] Combinations of three types of mutations were included in the FVIII sequences of the vCS series of constructs. The first amino acid change introduced into the FVIII sequence is the X1 mutation (TTYVNRSL (SEQ ID NO: 33); X. Xiao), which introduces an additional glycosylation site near the B-domain substituted linker. The X1 mutation is also referred to herein as the "m3" mutation. The second amino acid change made in the FVIII sequence includes the F328S (SPI, F309S SPE) mutation, an amino acid change known to improve secretion of FVIII (Swaaroop, J. Biol. Chem., 272:24121-24 (1997)). This mutation is also referred to herein as the "m1" mutation. The third change is the so-called X5 mutation, which is a combination of five amino acid changes in the A1 domain of the heavy chain that improves specific activity and secretion of BDD-FVIII (Cao et al., 2014; ASGCT abstract #460; details of mutations disclosed in oral presentation). The X5 mutation is also referred to herein as the "m2" mutation. Next, combinations of X1 and F328S (SPI, F309S SPE) were made, followed by combinations of X1 and X5, also referred to as "X6," and yet other combinations of X5 and F328S (SPI, F309S SPE) were made (Table 7).

[0383] Gene Synthesis and Cloning of the Vector Plasmids.

[0384] The plasmids were constructed by cloning different synthetic DNA fragments into the same vector backbone plasmid (pCh-BB01). DNA synthesis of the Refacto-type BDD-FVIII fragments with flanking AscI and NotI enzyme restriction sites were done by ThermoFischer Scientific

(Regensburg, Germany). The vector backbone contains two flanking AAV2-derived inverted terminal repeats (ITRs) that encompass a promoter/enhancer sequence derived from the liver-specific murine transthyretin gene, AscI and NotI enzyme restriction sites for insertion of the respective Refacto-type BDD-FVIII, and a synthetic polyA site. After ligation of the prepared vector backbone and insertions via the AscI and NotI sites, the resulting plasmids were amplified in milligram scale. The Refacto-type BDD-FVIII sequences of the constructs were verified by direct sequencing (Microsynth, Balgach, Switzerland). The cloning resulted in different plasmid constructs, as shown in FIG. **44**.

[0385] Small Scale Vector Preparations and Quantification by Quantitative PCR (qPCR).

[0386] AAV8-based vectors were prepared by the three plasmid transfection method essentially as described in Grieger et al. (2015, Supra). HEK293 suspensions cells were used for plasmid transfections using the corresponding FVIII vector plasmid, the helper plasmid pXX6X80 (carrying adenoviral helper genes) and the packaging plasmid pGSK2/8 (contributing the rep2 and cap8 genes). In the downstream process the cell pellet of a one liter culture was processed using iodixanol gradients as described above. The procedure resulted in vector preparations as outlined in Table 8. Vectors were quantified by qPCR using the universal qPCR procedure targeting the AAV2 inverted terminal repeats (Aurnhammer, HUMAN GENE THERAPY METHODS: Part B 23:18-28 (2012)). An accurately quantified vector plasmid carrying AAV2 Inverted terminal repeats served for preparing the standard curve.

[0387] AAV Vector Characterizations.

[0388] The integrity of the vector genome was analyzed by AAV agarose gel electrophoresis. The electrophoresis was done similar as described in Fagone et al. (Human Gene Therapy Methods, 23:1-7 (2012)). AAV vector preparations were incubated at 75° C. for 10 minutes in the presence of 0.5% SDS and then cooled down to room temperature. Approximately 1.5E10 vector genomes (vg) were loaded per lane on a 1% 1×TAE agarose gel and electrophoresed for 60 min at 7 V/cm of gel length. The gel was then stained in 2× GelRed (Biotium Cat#41003) solution and imaged by ChemiDoc™MP (Biorad). The results of a selection of vectors are shown in FIG. **45**. The viral vectors vCS04 (control), vCS17, vCS20, vCS24, vCS16 and vCS40 (control) show all the same-sized genome as a distinct band in the 5 kb range (FIG. **45**, lanes 2-7; arrow right side). Despite a vector size of approx. 5.2 kb, the genome is a homogenous band confirming correct packaging of the somewhat oversized genome (relative to an AAV wild-type genome of 4.7 kb).

[0389] In order to confirm purity of the vector and the expected pattern of capsid proteins, SDS PAGE followed by silver staining was performed with the vectors, as shown in FIG. **46**. As shown in the figure, the downstream purification procedure resulted in highly purified material displaying the expected protein pattern of VP1, VP2 and VP3 (FIG. **46** lanes 2-9; arrows right hand side). The SDS-PAGE procedure of AAV preparations was done according to standard procedures. The amounts of 1E10 vg per lane were separated on a 4-12% Bis-Tris (NuPAGE® Novex, Life Technologies) gel as per manufacturer's instructions. Silver staining was performed with a SilverQuest™ kit (Novex, Life Technologies) according to the instructions of the manufacturer.

[0390] In-Vivo Biopotency Screening of Vectors.

[0391] The different Refacto-type BDD-FVIII constructs were screened in mice. The assay was performed in C57Bl/6 FVIII knock-out (ko) mice (with 6-8 animals per group) by tail vein injection of 4E12 vector genomes (vg) per kilogram body weight of mouse. Blood was drawn 14 days after injection by retroorbital puncture and plasma was prepared and frozen using standard procedures. FVIII activity in mouse plasma was determined with a chromogenic assay from Technoclone with minor modifications (Technochrome FVIII, Technoclone, Vienna, Austria). In brief, the plasma sample was appropriately diluted and mixed with assay reagents, containing thrombin, activated factor IX (FIXa), phospholipids, factor X and calcium. Following FVIII activation by thrombin a complex with FIXa, phospholipids and calcium is formed. This complex activates FX to activated FX (FXa) which in turn cleaves para-nitroanilide (pNA) from the chromogenic substrate. The kinetics of pNA formation is measured at 405 nm. The rate is directly proportional to the FVIII concentration in the sample. FVIII concentrations are read from a reference curve and results are given in IU FVIII/milliliter.

[0392] The results of the mouse biopotency assay (day 14 expression data of FVIII in international units per milliliter [IU/ml] in mouse plasma and fold expression compared to the wild-type vCS40 control) are shown in Table 7. AAV vectors vCS19, vCS26 and vCS32 all contain the X1 glycosylation site in the CS01, CS04, and CS23 codon-altered backgrounds, respectively. As seen in Table 7, surprisingly high expression levels were obtained, as compared to the wild-type construct vCS40 (level defined as 1). vCS26, for instance, expressed 202-fold higher levels compared to the wild-type vCS40 vector. Another control construct for the X1-series of vectors, vCH111, that contains the X1 mutation in the Geneart codon context, showed a more modest increase in expression (12-fold).

[0393] Vectors vCS16, vCS28, and vCS34 all contain the F328S (SPI, F309S SPE) mutation enhancing secretion in the CS01, CS04, and CS23 codon-altered backgrounds, respectively. As seen in Table 7, high expression levels (45-93-fold higher than the wt vCS40 control) were obtained with vCS16 and vCS28.

[0394] Vectors vCS20, vCS24, and vCS33 contain the X5 mutation in the CS01, CS04, and CS23 codon-altered backgrounds, respectively. The best performing variant in the X5 series was vCS20, achieving levels of >3 units/ml after day 14 and a 121-fold increase over the wt vCS40 control.

[0395] Vectors vCS17, vCS29, and vCS31 contain the combination of the X1 and F328S (SPI, F309S SPE) mutations in the CS01, CS04, and CS23 codon-altered backgrounds, respectively (Table 6). The vCS17 and vCS29 constructs achieved very high expression levels in the mouse studies (115 to 246-fold increase over the vCS40 control). Remarkably, in the FVIII KO mouse model used, the majority of mice treated with the vCS17 construct did not develop neutralizing antibodies over time, evidenced by increasing levels of FVIII at later time points (e.g., day 28 and day 42; data not shown). This is an unexpected finding, because in some other constructs the expression levels began to decrease with time due to the formation of neutralizing antibodies. The CS01 background combined with the secretion-enhancing mutations F328S (SPI, F309S SPE) and X1 resulted in low immunogenicity induction.

[0396] Vectors vCS18, vCS27, and vCS35 contain the combination of the X1 and X5 mutations in the CS01, CS04,

and CS23 codon-altered backgrounds, respectively. The combination of these two mutations was also very efficient. A 145-fold increase over the vCS40 control could be achieved with vCS18, for example (Table 7).

[0397] Vectors vCS48 and vCS49 contain the combination of the X5 and F328S (SPI, F309S SPE) mutations in the CS01 and CS04 codon-altered backgrounds, respectively. The combination of these two mutations was also very efficient. One of the largest increases of all mutants, a 239-fold increase over the vCS40 control, could be achieved with vCS49 confirming the special value of the combinations including the F328S (SPI, F309S SPE) mutation.

[0398] A further surprising observation was that the mutant AAV vectors grew substantially better than the vCS40 construct harboring the wild-type BDD-FVIII codons. Sequence optimization resulted in a several-fold yield increase in vector production. In some of the best expressing constructs (e.g., vCS29, vCS17, vCS20, and vCS26) the increase in yields due to codon-alteration and/or mutant sequence was approximately 3-5-fold higher, as compared to the wild-type vector (Table 8).

[0399] Expression of BDD-FVIII in the plasma of FVIII-knock-out mice induced by the different AAV vector constructs is shown in Table 7. The constructs have the same vector backbone, however, encode different types of mutated FVIII, including different codon optimization backgrounds. Expression levels at day 14 were chosen because at this time point there is minimal influence of inhibitory antibodies usually seen in some animals in the mouse model at later times. N.d., not determined.

TABLE 7

In vivo biopotency data of vCS constructs.

#		Algorithm, mutations	Day 14 expression [IU/ml]	SD	Number of mice [n]	Fold expression
	Vector					
1	vCS19	CS01, X1	2.34	1.10	13	78
2	vCS26	CS04, X1	6.07	2.72	12	202
3	vCS32	CS23, X1	n.d.	—	—	—
4	vCS16	CS01, F328S	1.35	0.88	6	45
5	vCS28	CS04, F328S	2.78	0.92	7	93
6	vCS34	CS23, F328S	n.d.	—	—	—
7	vCS20	CS01, X5	3.62	1.96	21	121
8	vCS24	CS04, X5	0.79	0.89	18	26
9	vCS33	CS23, X5	n.d.	—	—	n.d.
10	vCS17	CS01, X1, F328S	3.44	1.92	20	115
11	vCS29	CS04, X1, F328S	7.39	2.64	9	246
12	vCS31	CS23, X1, F328S	n.d.			n.d.
13	vCS18	CS01, X1 + X5 (X6)	4.34	2.50	6	145
14	vCS27	CS04, X1 + X5 (X6)	8.03	3.97-	6-	268-
15	vCS35	CS23, X1 + X5 (X6)	n.d.	—	—	—
19	vCS48	CS01, X5, F328S	2.54	0.72	8	85
20	vCS49	CS04, X5, F328S	7.17	1.30	7	239
	controls					
16	vCS40	Human wild-type	0.03	0.03	12	1
17	vCh25	Geneart	0.13	0.12	18	4
18	vCh111	Geneart + X1	0.37	0.21	17	12

TABLE 8

Yields per liter cell culture (packaging efficiency) obtained with the different AAV vector constructs. The vectors were purified out of the cell pellets;

	con-struct	Algorithm, mutations	Vector conc. [vg/ml] × 10^{12}	Yields [vg/liter] × 10^{12}	Fold increase vs wt
1	vCS19	CS01, X1	9.71	36	3.22
2	vCS26	CS04, X1	5.93	32	2.87
3	vCS32	CS23, X1	n.d.	n.d.	n.d.
4	vCS16	CS01, F328S	6.51	29	2.56
5	vCS28	CS04, F328S	5.85	32	2.88
6	vCS34	CS23, F328S	n.d.	n.d.	n.d.
7	vCS20	CS01, X5	9.90	50	4.48
8	vCS24	CS04, X5	3.00	16	1.46
9	vCS33	CS23, X5	n.d.	n.d.	n.d.
10	vCS17	CS01, X1, F328S	8.94	37	3.34
11	vCS29	CS04, X1, F328S	7.42	53	4.72
12	vCS31	CS23, X1, F328S	n.d.	n.d.	n.d.
13	vCS18	CS01, X1 + X5 (X6)	21.20	53	4.75
14	vCS27	CS04, X1 + X5 (X6)	4.15	19	1.67
15	vCS35	CS23, X1 + X5 (X6)	n.d.	n.d.	n.d.
16	vCS48	CS01, X5, F328S	7.14	42.1	3.77
17	vCS49	CS04, X5, F328S	8.27	37.2	3.33
18	vCS40	Human wild-type	2.03	11	1.00

n.d., not determined.

[0400] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 109

<210> SEQ ID NO 1
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 1

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaaggc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg ggcagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccatggc ctctgaccca ctctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gttctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

-continued

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

agctatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccaggagc 2280

ttcagccaga atccacctgt cctgaaacgc caccagaggg agatcaccag gaccaccctc 2340

cagtctgacc aggaggagat tgactatgat gacaccattt ctgtggagat gaagaaagag 2400

gactttgaca tctatgacga ggacgagaac cagagcccaa ggagcttcca gaagaagacc 2460

aggcactact tcattgctgc tgtggagcgc ctgtgggact atggcatgag ctccagcccc 2520

catgtcctca ggaacagggc ccagtctggc tctgtgccac agttcaagaa agtggtcttc 2580

caagagttca ctgatggcag cttcacccag cccctgtaca gaggggagct gaatgagcac 2640

ctgggactcc tgggcccata catcagggct gaggtggagg acaacatcat ggtgaccttc 2700

cgcaaccagg cctccaggcc ctacagcttc tacagctccc tcatcagcta tgaggaggac 2760

cagaggcagg gggctgagcc acgcaagaac tttgtgaaac ccaatgaaac caagacctac 2820

ttctggaaag tccagcacca catggccccc accaaggatg agtttgactg caaggcctgg 2880

gcctacttct ctgatgtgga cctggagaag gatgtgcact ctggcctgat tggcccactc 2940

ctggtctgcc acaccaacac cctgaaccct gcccatggaa ggcaagtgac tgtgcaggag 3000

tttgccctct tcttcaccat ctttgatgaa accaagagct ggtacttcac tgagaacatg 3060

gagcgcaact gcagggcccc atgcaacatt cagatggagg accccacctt caaagagaac 3120

taccgcttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggcc 3180

caggaccaga ggatcaggtg gtacctgctt tctatgggct ccaatgagaa cattcactcc 3240

atccacttct ctgggcatgt cttcactgtg cgcaagaagg aggagtacaa gatggccctg 3300

tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc 3360

tggagggtgg agtgcctcat tggggagcac ctgcatgctg gcatgagcac cctgttcctg 3420

gtctacagca acaagtgcca gacccccctg ggaatggcct ctggccacat cagggacttc 3480

cagatcactg cctctggcca gtatggccag tgggccccca agctggccag gctccactac 3540

tctggatcca tcaatgcctg gagcaccaag gagccattca gctggatcaa agtggacctg 3600

ctggccccca tgatcatcca tggcatcaag acccaggggg ccaggcagaa gttctccagc 3660

ctgtacatca gccagttcat catcatgtac agcctggatg gcaagaaatg gcagacctac 3720

agaggcaact ccactggaac actcatggtc ttctttggca atgtggacag ctctggcatc 3780

aagcacaaca tcttcaaccc cccaatcatc gccagataca tcaggctgca ccccacccac 3840

tacagcatcc gcagcaccct caggatggag ctgatgggct gtgacctgaa ctcctgcagc 3900

atgcccctgg gcatggagag caaggccatt tctgatgccc agatcactgc ctccagctac 3960

ttcaccaaca tgtttgccac ctggagccca agcaaggcca ggctgcacct ccagggaagg 4020

agcaatgcct ggaggcccca ggtcaacaac ccaaaggagt ggctgcaggt ggacttccag 4080

aagaccatga aggtcactgg ggtgaccacc caggggtca agagcctgct caccagcatg 4140

tatgtgaagg agttcctgat cagctccagc caggatggcc accagtggac cctcttcttc 4200

-continued

cagaatggca aggtcaaggt gttccagggc aaccaggaca gcttcacccc tgtggtgaac 4260

agcctggacc ccccctcct gaccagatac ctgaggattc acccccagag ctgggtccac 4320

cagattgccc tgaggatgga ggtcctggga tgtgaggccc aggacctgta ctga 4374

<210> SEQ ID NO 2
<211> LENGTH: 1457
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 2

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met

-continued

```
305                 310                 315                 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
                325                 330                 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
            340                 345                 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
                405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
                485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
    530                 535                 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
                565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
                645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
            660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
        675                 680                 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
    690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705                 710                 715                 720
```

-continued

```
Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
               725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
            740                 745                 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
        755                 760                 765

Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln
    770                 775                 780

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
785                 790                 795                 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
               805                 810                 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
            820                 825                 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
        835                 840                 845

Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
    850                 855                 860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His
865                 870                 875                 880

Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile
               885                 890                 895

Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser
            900                 905                 910

Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
        915                 920                 925

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val
    930                 935                 940

Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
945                 950                 955                 960

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu
               965                 970                 975

Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His
            980                 985                 990

Gly Arg Gln Val Thr Val Gln Glu  Phe Ala Leu Phe Phe  Thr Ile Phe
        995                 1000                1005

Asp Glu  Thr Lys Ser Trp Tyr  Phe Thr Glu Asn Met  Glu Arg Asn
    1010                1015                1020

Cys Arg  Ala Pro Cys Asn Ile  Gln Met Glu Asp Pro  Thr Phe Lys
    1025                1030                1035

Glu Asn  Tyr Arg Phe His Ala  Ile Asn Gly Tyr Ile  Met Asp Thr
    1040                1045                1050

Leu Pro  Gly Leu Val Met Ala  Gln Asp Gln Arg Ile  Arg Trp Tyr
    1055                1060                1065

Leu Leu  Ser Met Gly Ser Asn  Glu Asn Ile His Ser  Ile His Phe
    1070                1075                1080

Ser Gly  His Val Phe Thr Val  Arg Lys Lys Glu Glu  Tyr Lys Met
    1085                1090                1095

Ala Leu  Tyr Asn Leu Tyr Pro  Gly Val Phe Glu Thr  Val Glu Met
    1100                1105                1110
```

-continued

```
Leu Pro  Ser Lys Ala Gly Ile  Trp Arg Val Glu Cys  Leu Ile Gly
    1115                1120                1125

Glu His  Leu His Ala Gly Met  Ser Thr Leu Phe Leu  Val Tyr Ser
    1130                1135                1140

Asn Lys  Cys Gln Thr Pro Leu  Gly Met Ala Ser Gly  His Ile Arg
    1145                1150                1155

Asp Phe  Gln Ile Thr Ala Ser  Gly Gln Tyr Gly Gln  Trp Ala Pro
    1160                1165                1170

Lys Leu  Ala Arg Leu His Tyr  Ser Gly Ser Ile Asn  Ala Trp Ser
    1175                1180                1185

Thr Lys  Glu Pro Phe Ser Trp  Ile Lys Val Asp Leu  Leu Ala Pro
    1190                1195                1200

Met Ile  Ile His Gly Ile Lys  Thr Gln Gly Ala Arg  Gln Lys Phe
    1205                1210                1215

Ser Ser  Leu Tyr Ile Ser Gln  Phe Ile Ile Met Tyr  Ser Leu Asp
    1220                1225                1230

Gly Lys  Lys Trp Gln Thr Tyr  Arg Gly Asn Ser Thr  Gly Thr Leu
    1235                1240                1245

Met Val  Phe Phe Gly Asn Val  Asp Ser Ser Gly Ile  Lys His Asn
    1250                1255                1260

Ile Phe  Asn Pro Pro Ile Ile  Ala Arg Tyr Ile Arg  Leu His Pro
    1265                1270                1275

Thr His  Tyr Ser Ile Arg Ser  Thr Leu Arg Met Glu  Leu Met Gly
    1280                1285                1290

Cys Asp  Leu Asn Ser Cys Ser  Met Pro Leu Gly Met  Glu Ser Lys
    1295                1300                1305

Ala Ile  Ser Asp Ala Gln Ile  Thr Ala Ser Ser Tyr  Phe Thr Asn
    1310                1315                1320

Met Phe  Ala Thr Trp Ser Pro  Ser Lys Ala Arg Leu  His Leu Gln
    1325                1330                1335

Gly Arg  Ser Asn Ala Trp Arg  Pro Gln Val Asn Asn  Pro Lys Glu
    1340                1345                1350

Trp Leu  Gln Val Asp Phe Gln  Lys Thr Met Lys Val  Thr Gly Val
    1355                1360                1365

Thr Thr  Gln Gly Val Lys Ser  Leu Leu Thr Ser Met  Tyr Val Lys
    1370                1375                1380

Glu Phe  Leu Ile Ser Ser Ser  Gln Asp Gly His Gln  Trp Thr Leu
    1385                1390                1395

Phe Phe  Gln Asn Gly Lys Val  Lys Val Phe Gln Gly  Asn Gln Asp
    1400                1405                1410

Ser Phe  Thr Pro Val Val Asn  Ser Leu Asp Pro Pro  Leu Leu Thr
    1415                1420                1425

Arg Tyr  Leu Arg Ile His Pro  Gln Ser Trp Val His  Gln Ile Ala
    1430                1435                1440

Leu Arg  Met Glu Val Leu Gly  Cys Glu Ala Gln Asp  Leu Tyr
    1445                1450                1455
```

<210> SEQ ID NO 3
<211> LENGTH: 2220
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

polynucleotide

<400> SEQUENCE: 3

gccaccagga gatactacct gggggctgtg gagctttctt gggactacat gcagtctgac 60

ctgggggagc tgcctgtgga tgccaggttc ccacccagag tgcccaaatc cttcccattc 120

aacacctctg tggtctacaa gaagaccctc tttgtggagt tcactgacca cctgttcaac 180

attgccaaac ccaggccacc ctggatggga ctcctgggac ccaccattca ggctgaggtg 240

tatgacactg tggtcatcac cctcaagaac atggcctccc accctgtgag cctgcatgct 300

gtgggggtca gctactggaa ggcctctgag ggggctgagt atgatgacca gacctcccag 360

agggagaagg aggatgacaa agtgttccct gggggcagcc acacctatgt gtggcaggtc 420

ctcaaggaga atggccccat ggcctctgac ccactctgcc tgacctactc ctacctttct 480

catgtggacc tggtcaagga cctcaactct ggactgattg gggccctgct ggtgtgcagg 540

gagggctccc tggccaaaga gaagacccag accctgcaca agttcattct cctgtttgct 600

gtctttgatg agggcaagag ctggcactct gaaaccaaga actccctgat gcaggacagg 660

gatgctgcct ctgccagggc ctggcccaag atgcacactg tgaatggcta tgtgaacagg 720

agcctgcctg gactcattgg ctgccacagg aaatctgtct actggcatgt gattggcatg 780

gggacaaccc ctgaggtgca ctccattttc ctggagggcc acaccttcct ggtcaggaac 840

cacagacagg ccagcctgga gatcagcccc atcaccttcc tcactgccca gaccctgctg 900

atggacctcg gacagttcct gctgttctgc cacatcagct cccaccagca tgatggcatg 960

gaggcctatg tcaaggtgga cagctgccct gaggagccac agctcaggat gaagaacaat 1020

gaggaggctg aggactatga tgatgacctg actgactctg agatggatgt ggtccgcttt 1080

gatgatgaca acagcccatc cttcattcag atcaggtctg tggccaagaa acaccccaag 1140

acctgggtgc actacattgc tgctgaggag gaggactggg actatgcccc actggtcctg 1200

gcccctgatg acaggagcta caagagccag tacctcaaca atggcccaca gaggattgga 1260

cgcaagtaca agaaagtcag gttcatggcc tacactgatg aaaccttcaa gaccagggag 1320

gccattcagc atgagtctgg catcctgggc ccactcctgt atggggaggt gggggacacc 1380

ctgctcatca tcttcaagaa ccaggcctcc aggccctaca acatctaccc acatggcatc 1440

actgatgtca ggcccctgta cagccgcagg ctgccaaagg gggtgaaaca cctcaaggac 1500

ttccccattc tgcctgggga gatcttcaag tacaagtgga ctgtcactgt ggaggatgga 1560

ccaaccaaat ctgaccccag gtgcctcacc agatactact ccagctttgt gaacatggag 1620

agggacctgg cctctggcct gattggccca ctgctcatct gctacaagga gtctgtggac 1680

cagaggggaa accagatcat gtctgacaag aggaatgtga ttctgttctc tgtctttgat 1740

gagaacagga gctggtacct gactgagaac attcagcgct tcctgcccaa ccctgctggg 1800

gtgcagctgg aggaccctga gttccaggcc agcaacatca tgcactccat caatggctat 1860

gtgtttgaca gcctccagct ttctgtctgc ctgcatgagg tggcctactg gtacattctt 1920

tctattgggg cccagactga cttcctttct gtcttcttct ctggctacac cttcaaacac 1980

aagatggtgt atgaggacac cctgaccctc ttcccattct ctggggagac tgtgttcatg 2040

agcatggaga accctggcct gtggattctg ggatgccaca actctgactt ccgcaacagg 2100

ggcatgactg ccctgctcaa agtctcctcc tgtgacaaga acactgggga ctactatgag 2160

-continued

gacagctatg aggacatctc tgcctacctg ctcagcaaga acaatgccat tgagcccagg 2220

<210> SEQ ID NO 4
<211> LENGTH: 2052
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 4

gagatcacca ggaccaccct ccagtctgac caggaggaga ttgactatga tgacaccatt 60

tctgtggaga tgaagaaaga ggactttgac atctatgacg aggacgagaa ccagagccca 120

aggagcttcc agaagaagac caggcactac ttcattgctg ctgtggagcg cctgtgggac 180

tatggcatga gctccagccc ccatgtcctc aggaacaggg cccagtctgg ctctgtgcca 240

cagttcaaga aagtggtctt ccaagagttc actgatggca gcttcaccca gcccctgtac 300

agaggggagc tgaatgagca cctgggactc ctgggcccat acatcagggc tgaggtggag 360

gacaacatca tggtgacctt ccgcaaccag gcctccaggc cctacagctt ctacagctcc 420

ctcatcagct atgaggagga ccagaggcag ggggctgagc cacgcaagaa ctttgtgaaa 480

cccaatgaaa ccaagaccta cttctggaaa gtccagcacc acatggcccc caccaaggat 540

gagtttgact gcaaggcctg ggcctacttc tctgatgtgg acctggagaa ggatgtgcac 600

tctggcctga ttggcccact cctggtctgc cacaccaaca ccctgaaccc tgcccatgga 660

aggcaagtga ctgtgcagga gtttgccctc ttcttcacca tctttgatga aaccaagagc 720

tggtacttca ctgagaacat ggagcgcaac tgcagggccc catgcaacat tcagatggag 780

gaccccacct tcaaagagaa ctaccgcttc catgccatca atggctacat catggacacc 840

ctgcctgggc ttgtcatggc ccaggaccag aggatcaggt ggtacctgct ttctatgggc 900

tccaatgaga acattcactc catccacttc tctgggcatg tcttcactgt gcgcaagaag 960

gaggagtaca agatggccct gtacaacctc taccctgggg tctttgagac tgtggagatg 1020

ctgccctcca aagctggcat ctggagggtg gagtgcctca ttggggagca cctgcatgct 1080

ggcatgagca ccctgttcct ggtctacagc aacaagtgcc agacccccct gggaatggcc 1140

tctggccaca tcagggactt ccagatcact gcctctggcc agtatggcca gtgggccccc 1200

aagctggcca ggctccacta ctctggatcc atcaatgcct ggagcaccaa ggagccattc 1260

agctggatca aagtggacct gctggccccc atgatcatcc atggcatcaa gacccagggg 1320

gccaggcaga agttctccag cctgtacatc agccagttca tcatcatgta cagcctggat 1380

ggcaagaaat ggcagaccta cagaggcaac tccactggaa cactcatggt cttctttggc 1440

aatgtggaca gctctggcat caagcacaac atcttcaacc ccccaatcat cgccagatac 1500

atcaggctgc accccaccca ctacagcatc cgcagcaccc tcaggatgga gctgatgggc 1560

tgtgacctga actcctgcag catgcccctg ggcatggaga gcaaggccat ttctgatgcc 1620

cagatcactg cctccagcta cttcaccaac atgtttgcca cctggagccc aagcaaggcc 1680

aggctgcacc tccagggaag gagcaatgcc tggaggcccc aggtcaacaa cccaaaggag 1740

tggctgcagg tggacttcca gaagaccatg aaggtcactg gggtgaccac ccaggggtc 1800

aagagcctgc tcaccagcat gtatgtgaag gagttcctga tcagctccag ccaggatggc 1860

caccagtgga ccctcttctt ccagaatggc aaggtcaagg tgttccaggg caaccaggac 1920

-continued

agcttcaccc ctgtggtgaa cagcctggac ccccccctcc tgaccagata cctgaggatt 1980

caccccaga gctgggtcca ccagattgcc ctgaggatgg aggtcctggg atgtgaggcc 2040

caggacctgt ac 2052

<210> SEQ ID NO 5
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 5

agcttctctc agaatccacc tgtcctgaag agacaccaga ga 42

<210> SEQ ID NO 6
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 6

agcttcagcc agaatccacc tgtcctgaaa cgccaccaga gg 42

<210> SEQ ID NO 7
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 7

agcttcagcc agaacccccc cgtgctgaag aggcaccaga gg 42

<210> SEQ ID NO 8
<211> LENGTH: 7827
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 8

tcgcgcgttt cggtgatgac ggtgaaaacc tctgacacat gcagctcccg gagacggtca 60

cagcttgtct gtaagcggat gccgggagca gacaagcccg tcagggcgcg tcagcgggtg 120

ttggcgggtg tcggggctgg cttaactatg cggcatcaga gcagattgta ctgagagtgc 180

accatatgcg gtgtgaaata ccgcacagat gcgtaaggag aaaataccgc atcaggcgcc 240

attcgccatt caggctgcgc aactgttggg aagggcgatc ggtgcgggcc tcttcgctat 300

tacgccagct ggcgaaaggg ggatgtgctg caaggcgatt aagttgggta acgccagggt 360

tttcccagtc acgacgttgt aaaacgacgg ccagtgaatt cctcgagatt taaatgacgt 420

tggccactcc ctctctgcgc gctcgctcgc tcactgaggc cgggcgacca aaggtcgccc 480

gacgcccggg ctttgcccgg gcggcctcag tgagcgagcg agcgcgcaga gagggagtgg 540

ccaactccat cactaggggt tcctgagttt aaacttcgtc gacgattcga gcttgggctg 600

-continued

caggtcgagg gcactgggag gatgttgagt aagatggaaa actactgatg acccttgcag 660

agacagagta ttaggacatg tttgaacagg ggccgggcga tcagcaggta gctctagagg 720

atccccgtct gtctgcacat ttcgtagagc gagtgttccg atactctaat ctccctaggc 780

aaggttcata tttgtgtagg ttacttattc tccttttgtt gactaagtca ataatcagaa 840

tcagcaggtt tggagtcagc ttggcaggga tcagcagcct gggttggaag gaggggtat 900

aaaagcccct tcaccaggag aagccgtcac acagactagg cgcgccaccg ccaccatgca 960

gattgagctg agcacctgct tcttcctgtg cctgctgagg ttctgcttct ctgccaccag 1020

gagatactac ctgggggctg tggagctttc ttgggactac atgcagtctg acctggggga 1080

gctgcctgtg gatgccaggt tcccacccag agtgcccaaa tccttcccat tcaacacctc 1140

tgtggtctac aagaagaccc tctttgtgga gttcactgac cacctgttca acattgccaa 1200

acccaggcca ccctggatgg gactcctggg acccaccatt caggctgagg tgtatgacac 1260

tgtggtcatc accctcaaga acatggcctc ccaccctgtg agcctgcatg ctgtgggggt 1320

cagctactgg aaggcctctg agggggctga gtatgatgac cagacctccc agagggagaa 1380

ggaggatgac aaagtgttcc ctgggggcag ccacacctat gtgtggcagg tcctcaagga 1440

gaatggcccc atggcctctg acccactctg cctgacctac tcctaccttt ctcatgtgga 1500

cctggtcaag gacctcaact ctggactgat tggggccctg ctggtgtgca gggagggctc 1560

cctggccaaa gagaagaccc agaccctgca caagttcatt ctcctgtttg ctgtctttga 1620

tgagggcaag agctggcact ctgaaaccaa gaactccctg atgcaggaca gggatgctgc 1680

ctctgccagg gcctggccca agatgcacac tgtgaatggc tatgtgaaca ggagcctgcc 1740

tggactcatt ggctgccaca ggaaatctgt ctactggcat gtgattggca tggggacaac 1800

ccctgaggtg cactccattt tcctggaggg ccacaccttc ctggtcagga accacagaca 1860

ggccagcctg gagatcagcc ccatcacctt cctcactgcc cagaccctgc tgatggacct 1920

cggacagttc ctgctgttct gccacatcag ctcccaccag catgatggca tggaggccta 1980

tgtcaaggtg gacagctgcc ctgaggagcc acagctcagg atgaagaaca atgaggaggc 2040

tgaggactat gatgatgacc tgactgactc tgagatggat gtggtccgct ttgatgatga 2100

caacagccca tccttcattc agatcaggtc tgtggccaag aaacacccca agacctgggt 2160

gcactacatt gctgctgagg aggaggactg ggactatgcc ccactggtcc tggcccctga 2220

tgacaggagc tacaagagcc agtacctcaa caatggccca cagaggattg gacgcaagta 2280

caagaaagtc aggttcatgg cctacactga tgaaaccttc aagaccaggg aggccattca 2340

gcatgagtct ggcatcctgg gcccactcct gtatggggag gtgggggaca ccctgctcat 2400

catcttcaag aaccaggcct ccaggcccta caacatctac ccacatggca tcactgatgt 2460

caggcccctg tacagccgca ggctgccaaa gggggtgaaa cacctcaagg acttccccat 2520

tctgcctggg gagatcttca agtacaagtg gactgtcact gtggaggatg gaccaaccaa 2580

atctgacccc aggtgcctca ccagatacta ctccagcttt gtgaacatgg agagggacct 2640

ggcctctggc ctgattggcc cactgctcat ctgctacaag gagtctgtgg accagagggg 2700

aaaccagatc atgtctgaca agaggaatgt gattctgttc tctgtctttg atgagaacag 2760

gagctggtac ctgactgaga acattcagcg cttcctgccc aaccctgctg gggtgcagct 2820

ggaggaccct gagttccagg ccagcaacat catgcactcc atcaatggct atgtgtttga 2880

-continued

cagcctccag ctttctgtct gcctgcatga ggtggcctac tggtacattc tttctattgg 2940

ggcccagact gacttccttt ctgtcttctt ctctggctac accttcaaac acaagatggt 3000

gtatgaggac accctgaccc tcttcccatt ctctggggag actgtgttca tgagcatgga 3060

gaaccctggc ctgtggattc tgggatgcca caactctgac ttccgcaaca ggggcatgac 3120

tgccctgctc aaagtctcct cctgtgacaa gaacactggg gactactatg aggacagcta 3180

tgaggacatc tctgcctacc tgctcagcaa gaacaatgcc attgagccca ggagcttcag 3240

ccagaatcca cctgtcctga aacgccacca gagggagatc accaggacca ccctccagtc 3300

tgaccaggag gagattgact atgatgacac catttctgtg gagatgaaga aagaggactt 3360

tgacatctat gacgaggacg agaaccagag cccaaggagc ttccagaaga agaccaggca 3420

ctacttcatt gctgctgtgg agcgcctgtg ggactatggc atgagctcca gcccccatgt 3480

cctcaggaac agggcccagt ctggctctgt gccacagttc aagaaagtgg tcttccaaga 3540

gttcactgat ggcagcttca cccagcccct gtacagaggg gagctgaatg agcacctggg 3600

actcctgggc ccatacatca gggctgaggt ggaggacaac atcatggtga ccttccgcaa 3660

ccaggcctcc aggccctaca gcttctacag ctccctcatc agctatgagg aggaccagag 3720

gcaggggggct gagccacgca agaactttgt gaaacccaat gaaaccaaga cctacttctg 3780

gaaagtccag caccacatgg cccccaccaa ggatgagttt gactgcaagg cctgggccta 3840

cttctctgat gtggacctgg agaaggatgt gcactctggc ctgattggcc cactcctggt 3900

ctgccacacc aacaccctga accctgccca tggaaggcaa gtgactgtgc aggagtttgc 3960

cctcttcttc accatctttg atgaaaccaa gagctggtac ttcactgaga acatggagcg 4020

caactgcagg gccccatgca acattcagat ggaggacccc accttcaaag agaactaccg 4080

cttccatgcc atcaatggct acatcatgga caccctgcct gggcttgtca tggcccagga 4140

ccagaggatc aggtggtacc tgctttctat gggctccaat gagaacattc actccatcca 4200

cttctctggg catgtcttca ctgtgcgcaa gaaggaggag tacaagatgg ccctgtacaa 4260

cctctaccct ggggtctttg agactgtgga gatgctgccc tccaaagctg gcatctggag 4320

ggtggagtgc ctcattgggg agcacctgca tgctggcatg agcaccctgt tcctggtcta 4380

cagcaacaag tgccagaccc ccctgggaat ggcctctggc cacatcaggg acttccagat 4440

cactgcctct ggccagtatg gccagtgggc ccccaagctg gccaggctcc actactctgg 4500

atccatcaat gcctggagca ccaaggagcc attcagctgg atcaaagtgg acctgctggc 4560

ccccatgatc atccatggca tcaagaccca gggggccagg cagaagttct ccagcctgta 4620

catcagccag ttcatcatca tgtacagcct ggatggcaag aaatggcaga cctacagagg 4680

caactccact ggaacactca tggtcttctt tggcaatgtg gacagctctg gcatcaagca 4740

caacatcttc aacccccaa tcatcgccag atacatcagg ctgcacccca cccactacag 4800

catccgcagc accctcagga tggagctgat gggctgtgac ctgaactcct gcagcatgcc 4860

cctgggcatg gagagcaagg ccatttctga tgcccagatc actgcctcca gctacttcac 4920

caacatgttt gccacctgga gcccaagcaa ggccaggctg cacctccagg gaaggagcaa 4980

tgcctggagg ccccaggtca acaacccaaa ggagtggctg caggtggact tccagaagac 5040

catgaaggtc actggggtga ccacccaggg ggtcaagagc ctgctcacca gcatgtatgt 5100

gaaggagttc ctgatcagct ccagccagga tggccaccag tggaccctct tcttccagaa 5160

-continued

tggcaaggtc aaggtgttcc agggcaacca ggacagcttc acccctgtgg tgaacagcct 5220

ggaccccccc ctcctgacca gatacctgag gattcacccc cagagctggg tccaccagat 5280

tgccctgagg atggaggtcc tgggatgtga ggcccaggac ctgtactgat gacgagcggc 5340

cgctcttagt agcagtatcg ataataaaag atctttattt tcattagatc tgtgtgttgg 5400

ttttttgtgt gttaattaag ctcgcgaagg aacccctagt gatggagttg gccactccct 5460

ctctgcgcgc tcgctcgctc actgaggccg ggcgaccaaa ggtcgcccga cgcccgggct 5520

ttgcccgggc ggcctcagtg agcgagcgag cgcgcagaga gggagtggcc aagacgattt 5580

aaatgacaag cttggcgtaa tcatggtcat agctgtttcc tgtgtgaaat tgttatccgc 5640

tcacaattcc acacaacata cgagccggaa gcataaagtg taaagcctgg ggtgcctaat 5700

gagtgagcta actcacatta attgcgttgc gctcactgcc cgctttccag tcgggaaacc 5760

tgtcgtgcca gctgcattaa tgaatcggcc aacgcgcggg gagaggcggt ttgcgtattg 5820

ggcgctcttc cgcttcctcg ctcactgact cgctgcgctc ggtcgttcgg ctgcggcgag 5880

cggtatcagc tcactcaaag gcggtaatac ggttatccac agaatcaggg gataacgcag 5940

gaaagaacat gtgagcaaaa ggccagcaaa aggccaggaa ccgtaaaaag gccgcgttgc 6000

tggcgttttt ccataggctc cgccccctg acgagcatca caaaaatcga cgctcaagtc 6060

agaggtggcg aaacccgaca ggactataaa gataccaggc gtttccccct ggaagctccc 6120

tcgtgcgctc tcctgttccg accctgccgc ttaccggata cctgtccgcc tttctccctt 6180

cgggaagcgt ggcgctttct catagctcac gctgtaggta tctcagttcg gtgtaggtcg 6240

ttcgctccaa gctgggctgt gtgcacgaac cccccgttca gcccgaccgc tgcgccttat 6300

ccggtaacta tcgtcttgag tccaacccgg taagacacga cttatcgcca ctggcagcag 6360

ccactggtaa caggattagc agagcgaggt atgtaggcgg tgctacagag ttcttgaagt 6420

ggtggcctaa ctacggctac actagaagaa cagtatttgg tatctgcgct ctgctgaagc 6480

cagttacctt cggaaaaaga gttggtagct cttgatccgg caaacaaacc accgctggta 6540

gcggtggttt ttttgtttgc aagcagcaga ttacgcgcag aaaaaaagga tctcaagaag 6600

atcctttgat cttttctacg gggtctgacg ctcagtggaa cgaaaactca cgttaaggga 6660

ttttggtcat gagattatca aaaaggatct tcacctagat ccttttaaat taaaaatgaa 6720

gttttaaatc aatctaaagt atatatgagt aaacttggtc tgacagttac caatgcttaa 6780

tcagtgaggc acctatctca gcgatctgtc tatttcgttc atccatagtt gcctgactcc 6840

ccgtcgtgta gataactacg atacgggagg gcttaccatc tggccccagt gctgcaatga 6900

taccgcgaga cccacgctca ccggctccag atttatcagc aataaaccag ccagccggaa 6960

gggccgagcg cagaagtggt cctgcaactt tatccgcctc catccagtct attaattgtt 7020

gccgggaagc tagagtaagt agttcgccag ttaatagttt gcgcaacgtt gttgccattg 7080

ctacaggcat cgtggtgtca cgctcgtcgt ttggtatggc ttcattcagc tccggttccc 7140

aacgatcaag gcgagttaca tgatccccca tgttgtgcaa aaaagcggtt agctccttcg 7200

gtcctccgat cgttgtcaga agtaagttgg ccgcagtgtt atcactcatg gttatggcag 7260

cactgcataa ttctcttact gtcatgccat ccgtaagatg cttttctgtg actggtgagt 7320

actcaaccaa gtcattctga gaatagtgta tgcggcgacc gagttgctct tgcccggcgt 7380

caatacggga taataccgcg ccacatagca gaactttaaa agtgctcatc attggaaaac 7440

-continued

gttcttcggg gcgaaaactc tcaaggatct taccgctgtt gagatccagt tcgatgtaac 7500

ccactcgtgc acccaactga tcttcagcat cttttacttt caccagcgtt tctgggtgag 7560

caaaaacagg aaggcaaaat gccgcaaaaa agggaataag ggcgacacgg aaatgttgaa 7620

tactcatact cttccttttt caatattatt gaagcattta tcagggttat tgtctcatga 7680

gcggatacat atttgaatgt atttagaaaa ataaacaaat aggggttccg cgcacatttc 7740

cccgaaaagt gccacctgac gtctaagaaa ccattattat catgacatta acctataaaa 7800

ataggcgtat cacgaggccc tttcgtc 7827

<210> SEQ ID NO 9
<211> LENGTH: 4332
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 9

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaaggc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg ggcagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccatggc ctctgaccca ctctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gttctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

-continued

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

agctatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccagggag 2280

atcaccagga ccaccctcca gtctgaccag gaggagattg actatgatga caccatttct 2340

gtggagatga agaaagagga ctttgacatc tatgacgagg acgagaacca gagcccaagg 2400

agcttccaga agaagaccag gcactacttc attgctgctg tggagcgcct gtgggactat 2460

ggcatgagct ccagccccca tgtcctcagg aacagggccc agtctggctc tgtgccacag 2520

ttcaagaaag tggtcttcca agagttcact gatggcagct tcacccagcc cctgtacaga 2580

ggggagctga atgagcacct gggactcctg ggcccataca tcagggctga ggtggaggac 2640

aacatcatgg tgaccttccg caaccaggcc tccaggccct acagcttcta cagctccctc 2700

atcagctatg aggaggacca gaggcagggg gctgagccac gcaagaactt tgtgaaaccc 2760

aatgaaacca agacctactt ctggaaagtc cagcaccaca tggcccccac caaggatgag 2820

tttgactgca aggcctgggc ctacttctct gatgtggacc tggagaagga tgtgcactct 2880

ggcctgattg gcccactcct ggtctgccac accaacaccc tgaaccctgc ccatggaagg 2940

caagtgactg tgcaggagtt tgccctcttc ttcaccatct ttgatgaaac caagagctgg 3000

tacttcactg agaacatgga gcgcaactgc agggccccat gcaacattca gatggaggac 3060

cccaccttca aagagaacta ccgcttccat gccatcaatg gctacatcat ggacaccctg 3120

cctgggcttg tcatggccca ggaccagagg atcaggtggt acctgctttc tatgggctcc 3180

aatgagaaca ttcactccat ccacttctct gggcatgtct tcactgtgcg caagaaggag 3240

gagtacaaga tggccctgta caacctctac cctggggtct ttgagactgt ggagatgctg 3300

ccctccaaag ctggcatctg gagggtggag tgcctcattg gggagcacct gcatgctggc 3360

atgagcaccc tgttcctggt ctacagcaac aagtgccaga ccccctgggg aatggcctct 3420

ggccacatca gggacttcca gatcactgcc tctggccagt atggccagtg ggcccccaag 3480

ctggccaggc tccactactc tggatccatc aatgcctgga gcaccaagga gccattcagc 3540

tggatcaaag tggacctgct ggcccccatg atcatccatg gcatcaagac ccaggggcc 3600

aggcagaagt tctccagcct gtacatcagc cagttcatca tcatgtacag cctggatggc 3660

aagaaatggc agacctacag aggcaactcc actggaacac tcatggtctt ctttggcaat 3720

gtggacagct ctggcatcaa gcacaacatc ttcaaccccc caatcatcgc cagatacatc 3780

-continued

aggctgcacc ccacccacta cagcatccgc agcaccctca ggatggagct gatgggctgt 3840

gacctgaact cctgcagcat gcccctgggc atggagagca aggccatttc tgatgcccag 3900

atcactgcct ccagctactt caccaacatg tttgccacct ggagcccaag caaggccagg 3960

ctgcacctcc agggaaggag caatgcctgg aggccccagg tcaacaaccc aaaggagtgg 4020

ctgcaggtgg acttccagaa gaccatgaag gtcactgggg tgaccaccca gggggtcaag 4080

agcctgctca ccagcatgta tgtgaaggag ttcctgatca gctccagcca ggatggccac 4140

cagtggaccc tcttcttcca gaatggcaag gtcaaggtgt tccagggcaa ccaggacagc 4200

ttcacccctg tggtgaacag cctggacccc cccctcctga ccagatacct gaggattcac 4260

ccccagagct gggtccacca gattgccctg aggatggagg tcctgggatg tgaggcccag 4320

gacctgtact ga 4332

<210> SEQ ID NO 10
<211> LENGTH: 1443
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 10

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225 230 235 240

-continued

```
Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
                245                 250                 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
            260                 265                 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
        275                 280                 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
    290                 295                 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305                 310                 315                 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
                325                 330                 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
            340                 345                 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
                405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
                485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
    530                 535                 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
                565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
```

-continued

```
               645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
           660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
       675                 680                 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
   690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705                 710                 715                 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
               725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
           740                 745                 750

Asn Asn Ala Ile Glu Pro Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser
       755                 760                 765

Asp Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys
   770                 775                 780

Lys Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg
785                 790                 795                 800

Ser Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg
               805                 810                 815

Leu Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg
           820                 825                 830

Ala Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu
       835                 840                 845

Phe Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn
   850                 855                 860

Glu His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp
865                 870                 875                 880

Asn Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe
               885                 890                 895

Tyr Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu
           900                 905                 910

Pro Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp
       915                 920                 925

Lys Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys
   930                 935                 940

Ala Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser
945                 950                 955                 960

Gly Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro
               965                 970                 975

Ala His Gly Arg Gln Val Thr Val Gln Glu Phe Ala Leu Phe Phe Thr
           980                 985                 990

Ile Phe Asp Glu Thr Lys Ser Trp  Tyr Phe Thr Glu Asn  Met Glu Arg
       995                 1000                1005

Asn Cys  Arg Ala Pro Cys Asn  Ile Gln Met Glu Asp  Pro Thr Phe
   1010                1015                1020

Lys Glu  Asn Tyr Arg Phe His  Ala Ile Asn Gly Tyr  Ile Met Asp
   1025                1030                1035

Thr Leu  Pro Gly Leu Val Met  Ala Gln Asp Gln Arg  Ile Arg Trp
   1040                1045                1050
```

-continued

```
Tyr Leu  Leu Ser Met Gly Ser  Asn Glu Asn Ile His  Ser Ile His
    1055                1060                1065

Phe Ser  Gly His Val Phe Thr  Val Arg Lys Lys Glu  Glu Tyr Lys
    1070                1075                1080

Met Ala  Leu Tyr Asn Leu Tyr  Pro Gly Val Phe Glu  Thr Val Glu
    1085                1090                1095

Met Leu  Pro Ser Lys Ala Gly  Ile Trp Arg Val Glu  Cys Leu Ile
    1100                1105                1110

Gly Glu  His Leu His Ala Gly  Met Ser Thr Leu Phe  Leu Val Tyr
    1115                1120                1125

Ser Asn  Lys Cys Gln Thr Pro  Leu Gly Met Ala Ser  Gly His Ile
    1130                1135                1140

Arg Asp  Phe Gln Ile Thr Ala  Ser Gly Gln Tyr Gly  Gln Trp Ala
    1145                1150                1155

Pro Lys  Leu Ala Arg Leu His  Tyr Ser Gly Ser Ile  Asn Ala Trp
    1160                1165                1170

Ser Thr  Lys Glu Pro Phe Ser  Trp Ile Lys Val Asp  Leu Leu Ala
    1175                1180                1185

Pro Met  Ile Ile His Gly Ile  Lys Thr Gln Gly Ala  Arg Gln Lys
    1190                1195                1200

Phe Ser  Ser Leu Tyr Ile Ser  Gln Phe Ile Ile Met  Tyr Ser Leu
    1205                1210                1215

Asp Gly  Lys Lys Trp Gln Thr  Tyr Arg Gly Asn Ser  Thr Gly Thr
    1220                1225                1230

Leu Met  Val Phe Phe Gly Asn  Val Asp Ser Ser Gly  Ile Lys His
    1235                1240                1245

Asn Ile  Phe Asn Pro Pro Ile  Ile Ala Arg Tyr Ile  Arg Leu His
    1250                1255                1260

Pro Thr  His Tyr Ser Ile Arg  Ser Thr Leu Arg Met  Glu Leu Met
    1265                1270                1275

Gly Cys  Asp Leu Asn Ser Cys  Ser Met Pro Leu Gly  Met Glu Ser
    1280                1285                1290

Lys Ala  Ile Ser Asp Ala Gln  Ile Thr Ala Ser Ser  Tyr Phe Thr
    1295                1300                1305

Asn Met  Phe Ala Thr Trp Ser  Pro Ser Lys Ala Arg  Leu His Leu
    1310                1315                1320

Gln Gly  Arg Ser Asn Ala Trp  Arg Pro Gln Val Asn  Asn Pro Lys
    1325                1330                1335

Glu Trp  Leu Gln Val Asp Phe  Gln Lys Thr Met Lys  Val Thr Gly
    1340                1345                1350

Val Thr  Thr Gln Gly Val Lys  Ser Leu Leu Thr Ser  Met Tyr Val
    1355                1360                1365

Lys Glu  Phe Leu Ile Ser Ser  Ser Gln Asp Gly His  Gln Trp Thr
    1370                1375                1380

Leu Phe  Phe Gln Asn Gly Lys  Val Lys Val Phe Gln  Gly Asn Gln
    1385                1390                1395

Asp Ser  Phe Thr Pro Val Val  Asn Ser Leu Asp Pro  Pro Leu Leu
    1400                1405                1410

Thr Arg  Tyr Leu Arg Ile His  Pro Gln Ser Trp Val  His Gln Ile
    1415                1420                1425
```

-continued

Ala Leu Arg Met Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
1430 1435 1440

<210> SEQ ID NO 11
<211> LENGTH: 4368
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 11

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaaggc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg ggcagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccatggc ctctgaccca ctctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gttctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

-continued

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

agctatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccaggagc 2280

ttcagccaga attccagaca ccccagcacc agggagatca ccaggaccac cctccagtct 2340

gaccaggagg agattgacta tgatgacacc atttctgtgg agatgaagaa agaggacttt 2400

gacatctatg acgaggacga gaaccagagc ccaaggagct tccagaagaa gaccaggcac 2460

tacttcattg ctgctgtgga gcgcctgtgg gactatggca tgagctccag cccccatgtc 2520

ctcaggaaca gggcccagtc tggctctgtg ccacagttca agaaagtggt cttccaagag 2580

ttcactgatg gcagcttcac ccagcccctg tacagagggg agctgaatga gcacctggga 2640

ctcctgggcc catacatcag ggctgaggtg gaggacaaca tcatggtgac cttccgcaac 2700

caggcctcca ggccctacag cttctacagc tccctcatca gctatgagga ggaccagagg 2760

caggggctg agccacgcaa gaactttgtg aaacccaatg aaaccaagac ctacttctgg 2820

aaagtccagc accacatggc ccccaccaag gatgagtttg actgcaaggc ctgggcctac 2880

ttctctgatg tggacctgga gaaggatgtg cactctggcc tgattggccc actcctggtc 2940

tgccacacca acaccctgaa ccctgcccat ggaaggcaag tgactgtgca ggagtttgcc 3000

ctcttcttca ccatctttga tgaaaccaag agctggtact tcactgagaa catggagcgc 3060

aactgcaggg ccccatgcaa cattcagatg gaggacccca ccttcaaaga gaactaccgc 3120

ttccatgcca tcaatggcta catcatggac accctgcctg ggcttgtcat ggcccaggac 3180

cagaggatca ggtggtacct gctttctatg ggctccaatg agaacattca ctccatccac 3240

ttctctgggc atgtcttcac tgtgcgcaag aaggaggagt acaagatggc cctgtacaac 3300

ctctaccctg gggtctttga gactgtggag atgctgccct ccaaagctgg catctggagg 3360

gtggagtgcc tcattgggga gcacctgcat gctggcatga gcaccctgtt cctggtctac 3420

agcaacaagt gccagacccc cctgggaatg gcctctggcc acatcaggga cttccagatc 3480

actgcctctg gccagtatgg ccagtgggcc cccaagctgg ccaggctcca ctactctgga 3540

tccatcaatg cctggagcac caaggagcca ttcagctgga tcaaagtgga cctgctggcc 3600

cccatgatca tccatggcat caagacccag ggggccaggc agaagttctc cagcctgtac 3660

atcagccagt tcatcatcat gtacagcctg gatggcaaga aatggcagac ctacagaggc 3720

aactccactg gaacactcat ggtcttcttt ggcaatgtgg acagctctgg catcaagcac 3780

aacatcttca acccccccaat catcgccaga tacatcaggc tgcaccccac ccactacagc 3840

atccgcagca ccctcaggat ggagctgatg ggctgtgacc tgaactcctg cagcatgccc 3900

ctgggcatgg agagcaaggc catttctgat gcccagatca ctgcctccag ctacttcacc 3960

aacatgtttg ccacctggag cccaagcaag gccaggctgc acctccaggg aaggagcaat 4020

gcctggaggc cccaggtcaa caacccaaag gagtggctgc aggtggactt ccagaagacc 4080

atgaaggtca ctggggtgac cacccagggg gtcaagagcc tgctcaccag catgtatgtg 4140

-continued

aaggagttcc tgatcagctc cagccaggat ggccaccagt ggaccctctt cttccagaat 4200

ggcaaggtca aggtgttcca gggcaaccag gacagcttca cccctgtggt gaacagcctg 4260

gacccccccc tcctgaccag atacctgagg attcaccccc agagctgggt ccaccagatt 4320

gccctgagga tggaggtcct gggatgtgag gcccaggacc tgtactga 4368

<210> SEQ ID NO 12
<211> LENGTH: 1455
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 12

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145 150 155 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
290 295 300

-continued

```
Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305                 310                 315                 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
                325                 330                 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
            340                 345                 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
                405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
                485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
    530                 535                 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
                565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
                645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
            660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
        675                 680                 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
    690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
```

-continued

```
705                 710                 715                 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
                725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
            740                 745                 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Ser Arg His Pro
        755                 760                 765

Ser Thr Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu
    770                 775                 780

Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe
785                 790                 795                 800

Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys
                805                 810                 815

Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr
            820                 825                 830

Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln Ser Gly
        835                 840                 845

Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr Asp Gly
    850                 855                 860

Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His Leu Gly
865                 870                 875                 880

Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile Met Val
                885                 890                 895

Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu
            900                 905                 910

Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn
        915                 920                 925

Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His
    930                 935                 940

His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr
945                 950                 955                 960

Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu Ile Gly
                965                 970                 975

Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg
            980                 985                 990

Gln Val Thr Val Gln Glu Phe Ala  Leu Phe Phe Thr Ile  Phe Asp Glu
        995                 1000                1005

Thr Lys  Ser Trp Tyr Phe Thr  Glu Asn Met Glu Arg  Asn Cys Arg
    1010                1015                1020

Ala Pro  Cys Asn Ile Gln Met  Glu Asp Pro Thr Phe  Lys Glu Asn
    1025                1030                1035

Tyr Arg  Phe His Ala Ile Asn  Gly Tyr Ile Met Asp  Thr Leu Pro
    1040                1045                1050

Gly Leu  Val Met Ala Gln Asp  Gln Arg Ile Arg Trp  Tyr Leu Leu
    1055                1060                1065

Ser Met  Gly Ser Asn Glu Asn  Ile His Ser Ile His  Phe Ser Gly
    1070                1075                1080

His Val  Phe Thr Val Arg Lys  Lys Glu Glu Tyr Lys  Met Ala Leu
    1085                1090                1095

Tyr Asn  Leu Tyr Pro Gly Val  Phe Glu Thr Val Glu  Met Leu Pro
    1100                1105                1110
```

-continued

```
Ser Lys  Ala Gly Ile Trp Arg  Val Glu Cys Leu Ile  Gly Glu His
    1115                1120                1125

Leu His  Ala Gly Met Ser Thr  Leu Phe Leu Val Tyr  Ser Asn Lys
    1130                1135                1140

Cys Gln  Thr Pro Leu Gly Met  Ala Ser Gly His Ile  Arg Asp Phe
    1145                1150                1155

Gln Ile  Thr Ala Ser Gly Gln  Tyr Gly Gln Trp Ala  Pro Lys Leu
    1160                1165                1170

Ala Arg  Leu His Tyr Ser Gly  Ser Ile Asn Ala Trp  Ser Thr Lys
    1175                1180                1185

Glu Pro  Phe Ser Trp Ile Lys  Val Asp Leu Leu Ala  Pro Met Ile
    1190                1195                1200

Ile His  Gly Ile Lys Thr Gln  Gly Ala Arg Gln Lys  Phe Ser Ser
    1205                1210                1215

Leu Tyr  Ile Ser Gln Phe Ile  Ile Met Tyr Ser Leu  Asp Gly Lys
    1220                1225                1230

Lys Trp  Gln Thr Tyr Arg Gly  Asn Ser Thr Gly Thr  Leu Met Val
    1235                1240                1245

Phe Phe  Gly Asn Val Asp Ser  Ser Gly Ile Lys His  Asn Ile Phe
    1250                1255                1260

Asn Pro  Pro Ile Ile Ala Arg  Tyr Ile Arg Leu His  Pro Thr His
    1265                1270                1275

Tyr Ser  Ile Arg Ser Thr Leu  Arg Met Glu Leu Met  Gly Cys Asp
    1280                1285                1290

Leu Asn  Ser Cys Ser Met Pro  Leu Gly Met Glu Ser  Lys Ala Ile
    1295                1300                1305

Ser Asp  Ala Gln Ile Thr Ala  Ser Ser Tyr Phe Thr  Asn Met Phe
    1310                1315                1320

Ala Thr  Trp Ser Pro Ser Lys  Ala Arg Leu His Leu  Gln Gly Arg
    1325                1330                1335

Ser Asn  Ala Trp Arg Pro Gln  Val Asn Asn Pro Lys  Glu Trp Leu
    1340                1345                1350

Gln Val  Asp Phe Gln Lys Thr  Met Lys Val Thr Gly  Val Thr Thr
    1355                1360                1365

Gln Gly  Val Lys Ser Leu Leu  Thr Ser Met Tyr Val  Lys Glu Phe
    1370                1375                1380

Leu Ile  Ser Ser Ser Gln Asp  Gly His Gln Trp Thr  Leu Phe Phe
    1385                1390                1395

Gln Asn  Gly Lys Val Lys Val  Phe Gln Gly Asn Gln  Asp Ser Phe
    1400                1405                1410

Thr Pro  Val Val Asn Ser Leu  Asp Pro Pro Leu Leu  Thr Arg Tyr
    1415                1420                1425

Leu Arg  Ile His Pro Gln Ser  Trp Val His Gln Ile  Ala Leu Arg
    1430                1435                1440

Met Glu  Val Leu Gly Cys Glu  Ala Gln Asp Leu Tyr
    1445                1450                1455
```

<210> SEQ ID NO 13
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 13

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc 60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg 120

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

ggagtctcat actggaaagc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

gagaaagagg atgacaaggt gttccctggg ggatctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccatggc atctgaccca ctctgcctga catactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc cattttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gttctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

-continued

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccagaagc 2280

ttctctcaga atccacctgt cctgaagaga caccagagag agatcaccag gacaaccctc 2340

cagtctgacc aggaagagat tgactatgat gacaccattt ctgtggagat gaagaaggag 2400

gactttgaca tctatgatga ggacgagaac cagtctccaa gatcattcca gaagaagaca 2460

agacactact tcattgctgc tgtggaaaga ctgtgggact atggcatgtc ttcctctccc 2520

catgtcctca ggaacagggc acagtctggc tctgtgccac agttcaagaa agtggtcttc 2580

caggagttca ctgatggctc attcacccag cccctgtaca gaggggaact gaatgagcac 2640

ctgggactcc tgggaccata catcagggct gaggtggaag acaacatcat ggtgacattc 2700

agaaaccagg cctccaggcc ctacagcttc tactcttccc tcatcagcta tgaggaagac 2760

cagagacaag gggctgagcc aagaaagaac tttgtgaaac ccaatgaaac caagacctac 2820

ttctggaaag tccagcacca catggcaccc accaaggatg agtttgactg caaggcctgg 2880

gcatacttct ctgatgtgga cctggagaaa gatgtgcact ctggcctgat tggcccactc 2940

ctggtctgcc acaccaacac cctgaaccct gcacatggaa ggcaagtgac tgtgcaggag 3000

tttgccctct tcttcaccat ctttgatgaa accaagtcat ggtacttcac tgagaacatg 3060

gagagaaact gcagagcacc atgcaacatt cagatggaag accccacctt caaggagaac 3120

tacaggttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggca 3180

caggaccaga gaatcagatg gtacctgctt tctatgggat ccaatgagaa cattcactcc 3240

atccacttct ctgggcatgt cttcactgtg agaaagaagg aggaatacaa gatggccctg 3300

tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc 3360

tggagggtgg aatgcctcat tggggagcac ctgcatgctg gcatgtcaac cctgttcctg 3420

gtctacagca acaagtgcca gacacccctg ggaatggcct ctggccacat cagggacttc 3480

cagatcactg cctctggcca gtatggccag tgggcaccca aactggccag gctccactac 3540

tctggctcca tcaatgcatg gtcaaccaag gagccattct cttggatcaa ggtggacctg 3600

ctggcaccca tgatcattca tggcatcaag acacaggggg caagacagaa attctcctct 3660

ctgtacatct cacagttcat catcatgtac tctctggatg gcaagaagtg gcagacatac 3720

agaggcaact ccactggcac cctcatggtc ttctttggca atgtggacag ctctggcatc 3780

aagcacaaca tcttcaaccc tcccatcatt gccagataca tcaggctgca ccccacccac 3840

tactcaatca gatcaaccct caggatggaa ctgatgggat gtgacctgaa ctcctgctca 3900

atgcccctgg gaatggagag caaggccatt tctgatgccc agatcactgc atcctcttac 3960

ttcaccaaca tgtttgccac ctggtcacca tcaaaagcca ggctgcacct ccagggaaga 4020

agcaatgcct ggagacccca ggtcaacaac ccaaaggaat ggctgcaagt ggacttccag 4080

aagacaatga aagtcactgg ggtgacaacc caggggtca agtctctgct cacctcaatg 4140

tatgtgaagg agttcctgat ctcttcctca caggatggcc accagtggac actcttcttc 4200

cagaatggca aagtcaaggt gttccagggc aaccaggact ctttcacacc tgtggtgaac 4260

tcactggacc ccccctcct gacaagatac ctgagaattc acccccagtc ttgggtccac 4320

cagattgccc tgagaatgga agtcctggga tgtgaggcac aagacctgta ctga 4374

-continued

<210> SEQ ID NO 14
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 14

atgcagatcg aactgagcac ttgcttcttc ctgtgtctcc tgcgcttttg cttctccgcc 60

acaaggagat actatctcgg tgccgtggag ctcagctggg actacatgca gagcgacttg 120

ggtgaactgc ctgtggacgc caggtttcca ccccgcgtgc ccaagagttt cccgttcaac 180

accagtgtcg tgtacaagaa aaccctcttc gtggaattca ccgaccacct gttcaacatc 240

gccaaaccgc gccctccctg gatggggctg ctcggcccga cgatccaggc tgaggtctat 300

gacacggtgg tgattaccct caagaacatg gctagccacc cggtgagcct gcacgccgtg 360

ggcgtgtcct attggaaagc gtccgagggt gcggagtacg atgaccagac ttcacagcgg 420

gagaaggaag acgacaaagt gttccccggg ggttcccaca cctatgtctg gcaggtcctg 480

aaggagaatg gtcctatggc ctccgaccca ttgtgcctca cctactctta cctaagccat 540

gtggatctcg tcaaggacct gaactcgggg ctgatcggcg ccctgctcgt gtgccgggag 600

ggctcactgg ccaaggagaa gacccaaact ctgcacaagt tcatcctgct gttcgcggta 660

ttcgacgagg ggaagtcctg gcactccgag accaagaaca gcctgatgca ggaccgcgac 720

gcagcctcgg cccgtgcgtg gccaaagatg cacaccgtga acggctacgt taacaggagc 780

ctacccggcc tgatcggctg ccaccgcaaa tcggtctact ggcatgtgat cggaatgggc 840

acaacgcccg aggtccacag tatcttcctc gagggccaca ctttcctggt ccggaatcac 900

cgccaggcca gcctggagat cagccccata acctttctga cggcgcagac cttactcatg 960

gatctcggcc agttcctcct gttctgccac atttcgtccc accagcacga tgggatggaa 1020

gcatatgtga aagtggactc ctgccccgag gaaccccagc ttaggatgaa gaacaatgag 1080

gaggccgagg actacgacga tgaccttacc gattcagaaa tggacgtagt acgctttgac 1140

gacgacaact ctccatcctt catacagatt cgctccgtcg ccaagaagca ccctaagact 1200

tgggtgcact acatcgcggc cgaggaggag gactgggatt atgctcccct ggtgctggcc 1260

cccgacgacc gcagctacaa gagccagtac ctgaataacg ggccccagcg catcggccgg 1320

aagtacaaga aagtgcggtt catggcttac acggacgaga ccttcaagac ccgggaggct 1380

atccagcatg agagcggcat cttggggccc ctcctgtacg gcgaagttgg agacacactg 1440

ctgatcatct tcaagaacca ggcgagcagg ccctacaaca tctaccccca cggcattacc 1500

gatgtccggc cgttgtacag ccgacggctg cccaagggcg tgaagcacct gaaggacttt 1560

ccgatcctgc cgggcgagat cttcaagtac aagtggactg tgaccgtgga ggatgggccg 1620

accaagagcg atccgcgctg cctgacccgt tactactcca gctttgtcaa tatggagcgc 1680

gacctcgcta gcggcttgat tggccctctg ctgatctgct acaaggagtc cgtggaccag 1740

aggggaatc agatcatgag tgacaagagg aacgtgatcc tgttctccgt gttcgacgaa 1800

aaccgcagct ggtatctcac cgagaatatc cagcgcttcc tgcccaaccc ggccggtgtg 1860

cagctggagg accccgagtt tcaggccagc aacatcatgc attctatcaa cggatatgtg 1920

tttgattccc tgcagctctc agtgtgtctg cacgaggtcg cctactggta tatcctcagc 1980

-continued

attggggcac agaccgactt cctgagcgtg ttcttctccg ggtatacctt caagcacaag 2040

atggtgtacg aggataccct gaccctgttc ccctttagcg gcgaaaccgt gtttatgtct 2100

atggagaacc ccgggctctg gatccttggc tgccataact ccgacttccg caaccgcgga 2160

atgaccgcgc tcctgaaagt gtcgagttgt gacaagaaca ccggcgacta ttacgaggac 2220

agttacgagg acatctctgc gtacctcctt agcaagaata acgccatcga gccaagatcc 2280

ttcagccaga acccccccagt gctgaagagg catcagcggg agatcacccg cacgaccctg 2340

cagtcggatc aggaggagat tgattacgac gacacgatca gtgtggagat gaagaaggag 2400

gacttcgaca tctacgacga agatgaaaac cagtcccctc ggtccttcca aaagaagacc 2460

cggcactact tcatcgccgc tgtggaacgc ctgtgggact atggaatgtc ttctagccct 2520

cacgttttga ggaaccgcgc ccagtcgggc agcgtgcccc agttcaagaa agtggtgttc 2580

caggagttca ccgacggctc cttcacccag ccactttacc ggggcgagct caatgaacat 2640

ctgggcctgc tgggacccta catcagggct gaggtggagg acaacatcat ggtgacattc 2700

cggaatcagg ccagcagacc atacagtttc tacagttcac tcatctccta cgaggaggac 2760

cagcgccagg gggctgaacc ccgtaagaac ttcgtgaagc caaacgaaac aaagacctac 2820

ttctggaagg tccagcacca catggcacct accaaggacg agttcgattg caaggcctgg 2880

gcctacttct ccgacgtgga cctggagaaa gatgtgcaca gcggcctgat tggccctctg 2940

ctggtgtgtc acacgaacac actcaaccct gcacacgggc ggcaggtcac tgtgcaggaa 3000

ttcgccctgt tctttaccat ctttgatgag acgaagtcct ggtatttcac cgaaaacatg 3060

gagaggaact gccgcgcacc ctgcaacatc cagatggaag atccgacatt caaggagaac 3120

taccggttcc atgccatcaa tggctacatc atggacaccc tgcctggcct cgtgatggcc 3180

caagaccagc gtatccgctg gtatctgctg tcgatgggct ccaacgagaa catccatagt 3240

atccacttca gcgggcatgt cttcacggtg aggaaaaagg aggagtacaa gatggcactg 3300

tacaacctct atcccggcgt gttcgagacc gtggagatgc tgccctccaa ggccggcatc 3360

tggagagtgg aatgcctgat cggcgagcac ctccacgctg ggatgtccac gctgttcctc 3420

gtttacagca ataagtgcca gacccctctg ggcatggcga gcggccacat ccgcgacttc 3480

cagattacag ccagcggcca gtacggtcag tgggctccaa agctggcccg tctgcactac 3540

tccggatcca tcaacgcctg gtccaccaag gaaccgttct cctggatcaa agtagacctg 3600

ctagccccca tgatcattca cggcatcaag acacaaggcg cccgacagaa gttctcgagc 3660

ctctatatct cccagttcat catcatgtat agcctggacg gaaagaagtg gcagacttac 3720

cgcggaaact cgacagggac cctgatggta ttcttcggta acgtggacag ctccggaatc 3780

aagcacaaca tcttcaaccc acccattatc gcccgctaca tccgcctgca ccccactcac 3840

tatagcatta ggtccaccct gcgaatggag ctcatgggct gtgacctgaa cagctgtagc 3900

atgcccctcg gcatggagtc taaggcgatc tccgacgcac agataacggc atcatcctac 3960

tttaccaaca tgttcgctac ctggtccccc tccaaggccc gactccacct gcaagggaga 4020

tccaacgcct ggcggccaca ggtcaacaat cccaaggagt ggctgcaagt ggactttcag 4080

aaaactatga aagtcaccgg agtgaccaca cagggagtga agtctctgct gaccagcatg 4140

tacgtgaagg agttcctcat ctccagttcg caggatggcc accagtggac gttgttcttc 4200

caaaacggta aagtcaaagt cttccaaggg aaccaggaca gctttacacc cgtcgtgaac 4260

-continued

tccctggacc ccccgcttct cactagatac ctccgcatcc accctcagag ctgggtgcac 4320

cagattgccc tgcgcatgga ggttctgggg tgtgaagccc aggacctgta ctaa 4374

<210> SEQ ID NO 15
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 15

atgcagattg agctctccac ctgcttcttt ctctgccttc ttcgcttctg cttttctgcc 60

acacgcaggt actatttggg agcagtggaa ctgagctggg attacatgca gagtgacctt 120

ggtgaacttc ctgtggacgc tcgttttcca cctagagttc ccaagtcctt ccccttcaac 180

acctcagtgg tctacaagaa aacgctgttt gtggagttca ctgaccacct cttcaacatt 240

gccaaaccaa gacccccttg gatgggattg ctgggaccca caatacaagc agaagtctac 300

gacacggtgg tgattaccct gaagaacatg gcgtcacacc ctgtttcact tcacgctgtt 360

ggggtcagtt attggaaagc ctcagagggt gcggaatacg atgatcaaac cagccagagg 420

gagaaggaag atgacaaggt ctttcctggg ggtagccata cctatgtttg gcaggtgctg 480

aaagagaatg ggcctatggc ctctgatccc ttgtgcctca catactctta cctgagtcac 540

gtcgacctgg tgaaagacct gaatagcggt ctgattggtg cactgcttgt ttgtagagag 600

gggagtttgg ccaaggagaa aactcagact ctccacaagt ttatcctcct gtttgctgtg 660

ttcgacgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca ggacagagat 720

gctgcatctg caagggcttg gccaaaaatg cacacagtga acggctatgt gaatcgatca 780

ctgccaggac tgataggctg tcatcgcaag tcagtgtatt ggcacgttat cgggatggga 840

acaactccag aagtgcacag catcttcctt gagggccaca ctttcctggt tcggaatcat 900

agacaggcca gccttgagat cagcccaatc acctttctga ctgcccaaac cttgctgatg 960

gatctgggac agttcctcct gttttgtcac atctcctccc accaacatga cgggatggag 1020

gcttatgtga aggtcgatag ctgtccggag gaaccacaac tgaggatgaa gaacaacgaa 1080

gaggcagagg actatgacga cgatctgact gacagtgaaa tggacgtggt tcggttcgac 1140

gatgacaatt ctccttcatt tatccagatc cgttccgtgg ccaagaagca ccccaagact 1200

tgggttcatt acatcgctgc tgaggaggag gattgggact acgcgccctt ggtgttggcc 1260

ccagacgatc gctcatacaa gagccagtac cttaacaatg gtccacaaag gatcggccgg 1320

aagtacaaga aggttagatt tatggcttat accgacgaga cttttaaaac tagggaagca 1380

attcagcatg aaagtggcat tcttggaccc ctgctgtatg gcgaggttgg cgacaccctg 1440

ctgattatct ttaagaacca ggcaagccgg ccctacaaca tctacccgca cggcataacc 1500

gatgtacgac ccctgtacag tcgcagactt cctaaagggg tgaaacacct gaaggacttc 1560

ccaattctgc ccggggagat cttcaagtat aaatggaccg tgacggttga ggatggtccc 1620

acaaagtccg atccgagatg ccttacccga tattattcca gcttcgtgaa catggaaagg 1680

gacctggcca gcgggctgat tggcccactg ctgatttgtt acaaggagtc tgtcgatcaa 1740

agaggaaacc aaataatgag cgacaaacgt aacgtcatcc tgttcagcgt ctttgatgag 1800

aatagaagct ggtacctcac agaaaatatt cagcggtttc tgcctaaccc cgcaggcgtc 1860

-continued

cagctggaag atcccgagtt ccaagcctca aacatcatgc atagcatcaa cggatacgta 1920

ttcgatagcc tgcagctgtc cgtctgtctc catgaagtgg catattggta catcctgagt 1980

atcggggcgc agaccgactt cctgagcgtg ttcttttctg gatacacgtt caaacacaaa 2040

atggtctatg aagataccct gactctgttt ccattctcag gagagacagt ctttatgagt 2100

atggaaaatc ctggactgtg gatcctgggc tgtcacaatt ctgattttcg gaacagaggc 2160

atgacagccc tgcttaaagt gagctcatgc gacaagaaca ccggtgatta ctacgaagat 2220

agctatgagg acatcagtgc gtatttgctc tccaagaaca acgctatcga gccacggtct 2280

ttcagtcaga atcctcccgt tctgaagcgg catcagcgcg aaataacacg cacaaccctt 2340

cagtcagacc aagaggaaat cgactacgat gatactatct ctgtggagat gaagaaggag 2400

gatttcgaca tttacgacga ggacgagaat cagtccccaa ggagctttca gaagaaaaca 2460

agacactatt tcattgccgc cgtggagcga ctgtgggact acggcatgtc tagctctccg 2520

catgtactta gaaatagggc acaaagcgga tccgtgcctc agtttaagaa agttgtcttt 2580

caggagttta cagatggctc cttcacccag cccttgtatc gcggggaact caatgaacac 2640

ctgggcctcc tgggtcctta tattagggcc gaagtcgagg acaatatcat ggtgaccttt 2700

aggaaccagg catctagacc ttactctttc tactcctccc tgatatccta tgaggaggac 2760

cagcggcaag gcgctgagcc tcggaagaac tttgtgaagc caaatgaaac caaaacatac 2820

ttttggaaag ttcagcacca catggctccc acgaaggacg aatttgactg taaagcctgg 2880

gcctacttct cagatgtaga tctcgagaaa gacgtgcact cagggctcat tggtcccctc 2940

ctggtctgtc atactaatac cctcaatcca gcacacggac gtcaggtaac cgtccaggaa 3000

tttgccctgt tctttaccat tttcgatgag actaaatcct ggtactttac cgaaaacatg 3060

gagaggaatt gcagagcccc atgcaacatc cagatggagg accctacctt caaagagaac 3120

tatcgcttcc atgccattaa cggttacatt atggatactc tcccaggact tgtgatggca 3180

caggatcagc ggataagatg gtatctgttg agcatgggct ccaacgagaa tattcacagc 3240

atccatttct ccggtcacgt gtttacagtg agaaagaaag aagagtacaa gatggctctg 3300

tataatctct atccaggcgt attcgaaacg gtggagatgt tgcctagcaa ggccggcatt 3360

tggcgagtag aatgccttat cggggaacat ctgcatgccg gaatgagcac gctcttcctg 3420

gtgtatagta acaagtgcca gactccgctg ggcatggcat ctggccatat acgggacttt 3480

cagattacgg ctagcgggca gtatgggcag tgggcaccca aacttgcgcg actgcactat 3540

tcaggctcta tcaatgcatg gtccaccaag gaacccttct cttggattaa ggtggacctt 3600

ttggcgccca tgataatcca tgggatcaaa acccagggcg ctcgtcagaa attctcatca 3660

ctctacatct ctcagttcat aataatgtat tcactggatg ggaagaaatg gcagacttac 3720

agaggaaaca gcaccgggac gctgatggtg ttctttggca acgtggacag cagcggcatc 3780

aaacacaaca tcttcaatcc tcccattatt gcccgttata ttagactgca tcccactcac 3840

tactctatac gcagcacact taggatggag ctcatgggat gcgacctgaa cagttgtagt 3900

atgcccttgg ggatggagtc caaagctata agcgacgcac aaattacagc tagctcttac 3960

tttacgaata tgttcgccac gtggagccca agcaaagccc ggctgcattt gcagggtcgg 4020

agtaatgctt ggcgcccaca ggtgaataac cctaaggaat ggttgcaagt agatttccag 4080

aaaactatga aggtaaccgg cgtcactaca cagggagtca agtccctctt gacctctatg 4140

-continued

tacgtcaagg agttcctgat tagcagcagt caggatgggc accaatggac actgttcttc 4200

cagaatggga aagttaaagt atttcagggt aaccaggact cctttacacc tgtggtgaat 4260

agcctcgacc caccctgct gacacgatac ctccgcatcc accctcagtc ttgggtgcat 4320

caaattgccc tgcgaatgga ggtgttggga tgcgaagctc aggacctcta ctga 4374

<210> SEQ ID NO 16
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 16

atgcagatcg aactctctac ttgcttcttc ctgtgccttc tgaggttctg cttctctgcc 60

actcgccgat attacctcgg ggccgtggag ttgagttggg actacatgca atcagatctg 120

ggcgaactcc ctgtggatgc ccgattccca ccgcgcgtgc ccaagtcttt cccatttaat 180

acttctgtgg tgtacaagaa gacattgttt gtggagttta ccgatcacct gttcaacatc 240

gccaaaccgc ggcccccatg gatgggtctg cttgggccca ccattcaagc ggaggtctat 300

gatacagtgg tgataacgct taagaacatg gcgagccacc cagtgtctct gcatgccgtt 360

ggtgtatcat attggaaggc cagcgaagga gcggagtacg atgaccagac ctctcagaga 420

gagaaggaag acgataaggt ttttcctggc ggaagtcata catatgtatg gcaggtcctg 480

aaagagaatg ggccgatggc ttctgacccc ctttgtctta cctatagtta tctgagccac 540

gtggacctgg tcaaggacct caacagtggt ctgattgggg ctctgcttgt ttgtagagag 600

ggtagcttgg ctaaggagaa aacccaaaca ctccataagt tcattttgct gttcgcggtg 660

ttcgacgagg gaaagagttg gcacagcgaa acaaagaatt cactgatgca agacagggac 720

gccgcttccg caagggcttg gcctaagatg catacggtga atgggtatgt gaaccggagc 780

ctcccggggc tgatcgggtg ccatcgcaag tctgtttact ggcacgtcat tggaatgggg 840

acaacgccag aggtacatag tatatttctt gaaggccaca cgttcctcgt acggaaccac 900

cgacaggctt ccctggagat aagccccatt acctttctga ccgctcagac tctgctgatg 960

gaccttggcc agtttctcct gttctgccat attagcagcc accagcacga cggtatggaa 1020

gcatacgtga aagtcgatag ctgtcctgag gagcctcagc tcagaatgaa gaacaacgag 1080

gaggccgaag actatgacga tgaccttaca gattccgaga tggacgtggt gcgctttgac 1140

gacgataaca gtcctagttt cattcaaatc agatccgtag ccaaaaagca tccaaagaca 1200

tgggtgcatt acattgcagc cgaagaggag gattgggatt atgcgcccct tgttctggct 1260

ccagatgaca ggagctataa gtcccagtac ttgaacaacg ggccacagcg aatcggtaga 1320

aaatataaga aggtaagatt catggcctac actgacgaaa catttaaaac cagggaagct 1380

atccaacacg aatctggaat tctcggccct ctgctctacg gtgaggtggg ggacaccttg 1440

ctgatcattt tcaaaaatca ggcatccagg ccttacaaca tataccccca tggcatcacc 1500

gatgtccgcc cgctgtattc cagaagactc cccaagggag tgaaacatct gaaagatttt 1560

cccatcctgc cgggcgagat ctttaaatac aaatggactg tgactgtaga ggacgggcct 1620

acaaaatcag acccacggtg cctgacaagg tattacagta gcttcgtcaa catggaacgc 1680

-continued

gacctcgcca gcggactcat tggcccactg ttgatctgtt acaaagagtc agtggatcag 1740

aggggaaatc agatcatgag cgataagaga aacgttatcc tgtttagtgt cttcgacgag 1800

aaccggtctt ggtaccttac tgagaacatc cagaggttcc tgccgaatcc ggctggcgtt 1860

cagctcgagg acccagagtt ccaggccagt aatataatgc actcaatcaa cggttatgtg 1920

ttcgatagcc tgcagctgag cgtctgcctc cacgaggtag cctattggta catattgtcc 1980

atcggggctc agaccgattt tctgtccgtg ttctttagcg ggtatacctt taaacataaa 2040

atggtctatg aagacaccct gaccctgttc ccattctccg gtgagactgt gttcatgtcc 2100

atggagaacc cagggctgtg gatcctgggg tgtcacaata gtgactttag gaatcgggga 2160

atgacggcac tgctgaaggt gagttcttgc gataaaaata caggagatta ctatgaggat 2220

agttacgagg atatcagtgc ctatctgctt tcaaaaaaca acgcaattga gccccggtct 2280

ttctcacaaa acccccccggt gctgaagcgc caccagcgcg aaattacccg gacaaccttg 2340

cagtccgacc aggaggaaat cgattatgac gatactatca gtgtagaaat gaaaaaggag 2400

gattttgata tttacgacga agacgagaac cagtctccgc gaagttttca gaagaaaacg 2460

cgacactact ttatagctgc cgtggaacga ctctgggatt atggcatgtc ctccagccct 2520

catgtcctta ggaatcgagc gcagagtggc tctgtgcctc agttcaaaaa ggttgtgttc 2580

caggaattca ccgacggctc atttacccag ccgctgtaca gaggcgaact caacgaacac 2640

cttgggctgc ttgggccata tattcgagca gaggtggaag ataatatcat ggtaaccttt 2700

agaaaccagg cgtcaagacc ctattccttc tacagttctc tgatcagcta cgaggaggac 2760

caaagacagg gagctgaacc caggaagaac tttgtgaaac ctaatgagac caagacctac 2820

ttctggaagg tccagcacca tatggcccca actaaagatg aattcgattg caaggcctgg 2880

gcttatttca gcgacgtgga tctcgaaaag gatgtgcaca gcgggttgat cggaccgctt 2940

ttggtgtgcc acacaaatac cctcaatcct gcccacgggc ggcaggtcac agttcaagag 3000

tttgcactct tctttacaat atttgacgag acaaagtcat ggtattttac agagaatatg 3060

gagagaaatt gtcgcgcacc ttgcaacatt cagatggagg accccacatt taaggagaat 3120

tacagatttc atgctatcaa tgggtacatt atggatactc tgcctggtct ggtcatggcc 3180

caggatcagc gcataaggtg gtacttgctg agcatgggat ctaatgagaa tatacacagc 3240

attcacttca gtggccacgt ttttactgtt agaaagaagg aggagtacaa aatggcgctc 3300

tacaaccttt acccgggtgt gtttgagaca gtggagatgc tgccaagcaa ggcaggcatc 3360

tggagggttg agtgtcttat tggggagcat ctgcatgctg gaatgtccac cctctttctt 3420

gtgtacagca ataagtgcca gacaccgctt ggcatggcca gcggccacat tagggacttt 3480

cagataactg ccagtggaca gtacggccag tgggctccca agcttgcaag actccactac 3540

tccggaagca taaacgcatg gagcaccaag gaacccttct cttggattaa ggtggacctg 3600

ctggcgccaa tgatcattca cggcataaaa acccaagggg cacgacagaa attttcatct 3660

ttgtatatta gtcagtttat catcatgtac agcttggatg gaaagaagtg gcagacgtac 3720

aggggcaatt ctacaggaac acttatggtg ttttttggga atgtcgattc cagcgggatc 3780

aaacataaca tcttcaatcc tcctattatc gcccgatata tccgcctgca ccctacgcat 3840

tactccatca ggtccacatt gagaatggaa ctgatggggt gcgacctgaa tagttgtagt 3900

atgccactgg gcatggagtc taaagccatc agcgatgcac agatcactgc cagctcttac 3960

-continued

ttcaccaaca tgtttgcaac ttggtccccc tctaaagctc gcctgcatct gcagggacgc 4020

tcaaatgcat ggcgaccaca ggtgaacaat ccaaaagagt ggctccaggt cgactttcag 4080

aagacaatga aggtaacagg agtgacaacc cagggtgtaa aaagcctcct tacgagtatg 4140

tacgttaagg agtttctgat ttctagctcc caggacggac accagtggac tctgttcttc 4200

cagaacggca aagtgaaggt atttcaggga aaccaggatt cttttacccc ggtagtgaat 4260

agcctggatc caccgttgct gacccgctat ctgagaattc atccacaatc ctgggtgcat 4320

cagattgccc tccggatgga agtgctcggc tgtgaagctc aggatctgta ttag 4374

<210> SEQ ID NO 17
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 17

atgcaaatag agctctccac ctgcttcttt ctgtgccttt tgcgattctg ctttagtgcc 60

accagaagat actacctggg tgcagtggaa ctgtcatggg actatatgca aagtgatctc 120

ggtgagctgc ctgtggacgc aagatttcct cctagagtgc caaaatcttt tccattcaac 180

acctcagtcg tgtacaaaaa gactctgttt gtagaattca cggatcacct tttcaacatc 240

gctaagccaa ggccaccctg gatgggtctg ctaggtccta ccatccaggc tgaggtttat 300

gatacagtgg tcattacact taagaacatg gcttcccatc ctgtcagtct tcatgctgtt 360

ggtgtatcct actggaaagc ttctgaggga gctgaatatg atgatcagac cagtcaaagg 420

gagaaagaag atgataaagt cttccctggt ggaagccata catatgtctg gcaggtcctg 480

aaagagaatg gtccaatggc ctctgaccca ctgtgcctta cctactcata tctttctcat 540

gtggacctgg taaaagactt gaattcaggc ctcattggag ccctactagt atgtagagaa 600

gggagtctgg ccaaggaaaa gacacagacc ttgcacaaat ttatactact ttttgctgta 660

tttgatgaag ggaaaagttg gcactcagaa acaaagaact ccttgatgca ggatagggat 720

gctgcatctg ctcgggcctg gcctaaaatg cacacagtca atggttatgt aaacaggtct 780

ctgccaggtc tgattggatg ccacaggaaa tcagtctatt ggcatgtgat tggaatgggc 840

accactcctg aagtgcactc aatattcctc gaaggtcaca catttcttgt gaggaaccat 900

cgccaggcgt ccttggaaat ctcgccaata actttcctta ctgctcaaac actcttgatg 960

gaccttggac agtttctact gttttgtcat atctcttccc accaacatga tggcatggaa 1020

gcttatgtca aagtagacag ctgtccagag gaaccccaac tacgaatgaa aaataatgaa 1080

gaagcggaag actatgatga tgatcttact gattctgaaa tggatgtggt caggtttgat 1140

gatgacaact ctccttcctt tatccaaatt cgctcagttg ccaagaagca tcctaaaact 1200

tgggtacatt acattgctgc tgaagaggag gactgggact atgctccctt agtcctcgcc 1260

cccgatgaca gaagttataa aagtcaatat ttgaacaatg gccctcagcg gattggtagg 1320

aagtacaaaa aagtccgatt tatggcatac acagatgaaa cctttaagac tcgtgaagct 1380

attcagcatg aatcaggaat cttgggacct ttactttatg gggaagttgg agacacactg 1440

ttgattatat ttaagaatca agcaagcaga ccatataaca tctaccctca cggaatcact 1500

gatgtccgtc ctttgtattc aaggagatta ccaaaaggtg taaaacattt gaaggatttt 1560

-continued

ccaattctgc caggagaaat attcaaatat aaatggacag tgactgtaga agatgggcca 1620

actaaatcag atcctcggtg cctgacccgc tattactcta gtttcgttaa tatggagaga 1680

gatctagctt caggactcat tggccctctc ctcatctgct acaaagaatc tgtagatcaa 1740

agaggaaacc agataatgtc agacaagagg aatgtcatcc tgttttctgt atttgatgag 1800

aaccgaagct ggtacctcac agagaatata caacgctttc tccccaatcc agctggagtg 1860

cagcttgagg atccagagtt ccaagcctcc aacatcatgc acagcatcaa tggctatgtt 1920

tttgatagtt tgcagttgtc agtttgtttg catgaggtgg catactggta cattctaagc 1980

attggagcac agactgactt cctttctgtc ttcttctctg gatatacctt caaacacaaa 2040

atggtctatg aagacacact caccctattc ccattctcag gagaaactgt cttcatgtcg 2100

atggaaaacc caggtctatg gattctgggg tgccacaact cagactttcg gaacagaggc 2160

atgaccgcct tactgaaggt ttctagttgt gacaagaaca ctggtgatta ttacgaggac 2220

agttatgaag atatttcagc atacttgctg agtaaaaaca atgccattga accaagaagc 2280

ttctcccaga atccaccagt cttgaaacgc catcaacggg aaataactcg tactactctt 2340

cagtcagatc aagaggaaat tgactatgat gataccatat cagttgaaat gaagaaggaa 2400

gattttgaca tttatgatga ggatgaaaat cagagccccc gcagctttca aaagaaaaca 2460

cgacactatt ttattgctgc agtggagagg ctctgggatt atgggatgag tagctcccca 2520

catgttctaa gaaacagggc tcagagtggc agtgtccctc agttcaagaa agttgttttc 2580

caggaattta ctgatggctc ctttactcag cccttatacc gtggagaact aaatgaacat 2640

ttgggactcc tggggccata tataagagca gaagttgaag ataatatcat ggtaactttc 2700

agaaatcagg cctctcgtcc ctattccttc tattctagcc ttatttctta tgaggaagat 2760

cagaggcaag gagcagaacc tagaaaaaac tttgtcaagc ctaatgaaac caaaacttac 2820

ttttggaaag tgcaacatca tatggcaccc actaaagatg agtttgactg caaagcctgg 2880

gcttatttct ctgatgttga cctggaaaaa gatgtgcact caggcctgat tggacccctt 2940

ctggtctgcc acactaacac actgaaccct gctcatggga gacaagtgac agtacaggaa 3000

tttgctctgt ttttcaccat ctttgatgag accaaaagct ggtacttcac tgaaaatatg 3060

gaaagaaact gcagggctcc ctgcaatatc cagatggaag atcccacttt taaagagaat 3120

tatcgcttcc atgcaatcaa tggctacata atggatacac tacctggctt agtaatggct 3180

caggatcaaa ggattcgatg gtatctgctc agcatgggca gcaatgaaaa catccattct 3240

attcatttca gtggacatgt gttcactgta cgaaaaaaag aggagtataa aatggcactg 3300

tacaatctct atccaggtgt ttttgagaca gtggaaatgt taccatccaa agctggaatt 3360

tggcgggtgg aatgccttat tggcgagcat ctacatgctg ggatgagcac acttttttctg 3420

gtgtacagca ataagtgtca gactcccctg ggaatggctt ctggacacat tagagatttt 3480

cagattacag cttcaggaca atatggacag tgggccccaa agctggccag acttcattat 3540

tccggatcaa tcaatgcctg gagcaccaag gagccctttt cttggatcaa ggtggatctg 3600

ttggcaccaa tgattattca cggcatcaag acccagggtg cccgtcagaa gttctccagc 3660

ctctacatct ctcagtttat catcatgtat agtcttgatg ggaagaagtg gcagacttat 3720

cgaggaaatt ccactggaac cttaatggtc ttctttggca atgtggattc atctgggata 3780

aaacacaata tttttaaccc tccaattatt gctcgataca tccgtttgca cccaactcat 3840

-continued

tatagcattc gcagcactct tcgcatggag ttgatgggct gtgatttaaa tagttgcagc 3900

atgccattgg gaatggagag taaagcaata tcagatgcac agattactgc ttcatcctac 3960

tttaccaata tgtttgccac ctggtctcct tcaaaagctc gacttcacct ccaagggagg 4020

agtaatgcct ggagacctca ggtgaataat ccaaaagagt ggctgcaagt ggacttccag 4080

aagacaatga aagtcacagg agtaactact cagggagtaa aatctctgct taccagcatg 4140

tatgtgaagg agttcctcat ctccagcagt caagatggcc atcagtggac tctcttttt 4200

cagaatggca aagtaaaggt ttttcaggga aatcaagact ccttcacacc tgtggtgaac 4260

tctctagacc caccgttact gactcgctac cttcgaattc acccccagag ttgggtgcac 4320

cagattgccc tgaggatgga ggttctgggc tgcgaggcac aggacctcta ctga 4374

<210> SEQ ID NO 18
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 18

atgcagatcg agctgtccac atgctttttt ctgtgcctgc tgcggttctg cttcagcgcc 60

acccggcggt actacctggg cgccgtggag ctgtcctggg actacatgca gagcgacctg 120

ggcgagctgc ccgtggacgc ccggttcccc cccagagtgc ccaagagctt ccccttcaac 180

accagcgtgg tgtacaagaa aaccctgttc gtggagttca ccgaccacct gttcaacatc 240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac 300

gacaccgtgg tgatcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg 360

ggcgtgagct actggaaggc ctccgagggc gccgagtacg acgaccagac cagccagcgg 420

gagaaagagg acgacaaagt ctttcctggc ggcagccaca cctacgtgtg gcaggtcctg 480

aaagaaaacg gccccatggc ctccgacccc ctgtgcctga cctacagcta cctgagccac 540

gtggacctgg tgaaggacct gaacagcggg ctgattgggg ccctgctggt ctgccgggag 600

ggcagcctgg ccaaagagaa aacccagacc ctgcacaagt tcatcctgct gttcgccgtg 660

ttcgacgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggaccgggac 720

gccgcctctg ccagagcctg gcccaagatg cacaccgtga acggctacgt gaacagaagc 780

ctgcccggcc tgattggctg ccaccggaag agcgtgtact ggcacgtgat cggcatgggc 840

accacacccg aggtgcacag catctttctg gaagggcaca cctttctggt gcggaaccac 900

cggcaggcca gcctggaaat cagccctatc accttcctga ccgcccagac actgctgatg 960

gacctgggcc agttcctgct gttttgccac atcagctctc accagcacga cggcatggaa 1020

gcctacgtga aggtggactc ctgccccgag gaaccccagc tgcggatgaa gaacaacgag 1080

gaagccgagg actacgacga cgacctgacc gacagcgaga tggacgtggt gcggttcgac 1140

gacgacaaca gccccagctt catccagatc agaagcgtgg ccaagaagca ccccaagacc 1200

tgggtgcact acatcgccgc cgaggaagag gactgggact acgccccct ggtgctggcc 1260

cccgacgaca gaagctacaa gagccagtac ctgaacaatg gcccccagcg gatcggccgg 1320

aagtacaaga aagtgcggtt catggcctac accgacgaga ccttcaagac ccgggaggcc 1380

-continued

atccagcacg agagcggcat cctgggcccc ctgctgtacg gcgaagtggg cgacacactg 1440

ctgatcatct tcaagaacca ggccagccgg ccctacaaca tctaccccca cggcatcacc 1500

gacgtgcggc ccctgtacag caggcggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggacggcccc 1620

accaagagcg accccagatg cctgacccgg tactacagca gcttcgtgaa catggaacgg 1680

gacctggcct ccgggctgat cggacctctg ctgatctgct acaaagaaag cgtggaccag 1740

cggggcaacc agatcatgag cgacaagcgg aacgtgatcc tgttcagcgt gttcgatgag 1800

aaccggtcct ggtatctgac cgagaacatc cagcggtttc tgcccaaccc tgccggggtg 1860

cagctggaag atcccgagtt ccaggccagc aacatcatgc actccatcaa tggctacgtg 1920

ttcgacagcc tgcagctgtc cgtgtgtctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgagcgtg ttcttcagcg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cctttcagcg gcgagaccgt gttcatgagc 2100

atggaaaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttccg gaaccggggc 2160

atgaccgccc tgctgaaggt gtccagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg atatcagcgc ctacctgctg tccaagaaca acgccatcga gcccagaagc 2280

ttcagccaga accccccctgt gctgaagcgg caccagagag agatcacccg gaccaccctg 2340

cagtccgacc aggaagagat cgattacgac gacaccatca gcgtggagat gaaaaaagaa 2400

gatttcgaca tctacgacga ggacgagaac cagagccccc ggtccttcca gaagaaaacc 2460

cggcactact ttatcgccgc cgtggagcgg ctgtgggact acggcatgag cagcagcccc 2520

cacgtgctgc ggaaccgggc ccagagcggc agcgtgcccc agttcaagaa agtggtgttc 2580

caggaattca ccgacggcag cttcacccag cccctgtacc ggggcgagct gaacgagcac 2640

ctggggctgc tggggcccta catcagggcc gaagtggagg acaacatcat ggtgaccttc 2700

cggaatcagg ccagcagacc ctactccttc tacagcagcc tgatcagcta cgaagaggac 2760

cagcggcagg gcgctgaacc ccggaagaac ttcgtgaagc ccaatgagac caagacctac 2820

ttctggaaag tgcagcacca catggccccc accaaggacg agttcgactg caaggcctgg 2880

gcctacttca gcgacgtgga tctggaaaag gacgtgcact ctggactgat tggccctctg 2940

ctggtgtgcc acaccaacac cctgaacccc gcccacggcc ggcaggtgac cgtgcaggaa 3000

ttcgccctgt tcttcaccat cttcgacgag accaagtcct ggtacttcac cgagaatatg 3060

gaacggaact gcagagcccc ctgcaacatc cagatggaag atcctacctt caaagagaac 3120

taccggttcc acgccatcaa cggctacatc atggacaccc tgcctggcct ggtgatggcc 3180

caggaccaga ggatccggtg gtatctgctg tccatgggca gcaacgagaa tatccacagc 3240

atccacttca gcggccacgt gttcaccgtg aggaagaaag aagagtacaa gatggccctg 3300

tacaacctgt accccggcgt gttcgagacc gtggagatgc tgcccagcaa ggccggcatc 3360

tggcgggtgg agtgtctgat cggcgagcac ctgcatgccg ggatgagcac cctgtttctg 3420

gtgtacagca acaagtgcca gacccccctg ggcatggcca gcggccacat ccgggacttc 3480

cagatcaccg cctccggcca gtacggccag tgggccccca agctggcccg gctgcactac 3540

agcggcagca tcaacgcctg gtccaccaaa gagcccttca gctggatcaa ggtggacctg 3600

ctggccccta tgatcatcca cggcattaag acccagggcg ccaggcagaa gttcagcagc 3660

-continued

```
ctgtacatca gccagttcat catcatgtac agcctggacg gcaagaagtg gcagacctac   3720

cggggcaaca gcaccggcac cctgatggtg ttcttcggca acgtggacag cagcggcatc   3780

aagcacaaca tcttcaaccc ccccatcatc gcccggtaca tccggctgca ccccacccac   3840

tacagcatca gatccaccct gcggatggaa ctgatgggct gcgacctgaa ctcctgcagc   3900

atgcctctgg gcatggaaag caaggccatc agcgacgccc agatcacagc cagcagctac   3960

ttcaccaaca tgttcgccac ctggtccccc tccaaggcca ggctgcacct gcagggccgg   4020

tccaacgcct ggcggcctca ggtgaacaac cccaaagaat ggctgcaggt ggactttcag   4080

aaaaccatga aggtgaccgg cgtgaccacc cagggcgtga aaagcctgct gaccagcatg   4140

tacgtgaaag agtttctgat cagcagcagc caggacggcc accagtggac cctgttcttt   4200

cagaacggca aggtgaaagt gttccagggc aaccaggact ccttcacccc cgtggtgaac   4260

tccctggacc ccccccctgct gacccgctac ctgcggatcc acccccagtc ttgggtgcac   4320

cagatcgccc tgaggatgga agtgctggga tgtgaggccc aggatctgta ctga         4374
```

<210> SEQ ID NO 19
<211> LENGTH: 2351
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

```
Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1               5                  10                  15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
            20                  25                  30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
        35                  40                  45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
    50                  55                  60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65                  70                  75                  80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
                85                  90                  95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
            100                 105                 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
        115                 120                 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
    130                 135                 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145                 150                 155                 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
                165                 170                 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
            180                 185                 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
        195                 200                 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
    210                 215                 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225                 230                 235                 240
```

-continued

```
Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
               245                 250                 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
            260                 265                 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
        275                 280                 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
    290                 295                 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305                 310                 315                 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
               325                 330                 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
            340                 345                 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
               405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
               485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
    530                 535                 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
               565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640
```

-continued

```
Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
                645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
            660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
        675                 680                 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
    690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705                 710                 715                 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
                725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
            740                 745                 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Ser Arg His Pro
        755                 760                 765

Ser Thr Arg Gln Lys Gln Phe Asn Ala Thr Thr Ile Pro Glu Asn Asp
    770                 775                 780

Ile Glu Lys Thr Asp Pro Trp Phe Ala His Arg Thr Pro Met Pro Lys
785                 790                 795                 800

Ile Gln Asn Val Ser Ser Ser Asp Leu Leu Met Leu Leu Arg Gln Ser
                805                 810                 815

Pro Thr Pro His Gly Leu Ser Leu Ser Asp Leu Gln Glu Ala Lys Tyr
            820                 825                 830

Glu Thr Phe Ser Asp Asp Pro Ser Pro Gly Ala Ile Asp Ser Asn Asn
        835                 840                 845

Ser Leu Ser Glu Met Thr His Phe Arg Pro Gln Leu His His Ser Gly
    850                 855                 860

Asp Met Val Phe Thr Pro Glu Ser Gly Leu Gln Leu Arg Leu Asn Glu
865                 870                 875                 880

Lys Leu Gly Thr Thr Ala Ala Thr Glu Leu Lys Lys Leu Asp Phe Lys
                885                 890                 895

Val Ser Ser Thr Ser Asn Asn Leu Ile Ser Thr Ile Pro Ser Asp Asn
            900                 905                 910

Leu Ala Ala Gly Thr Asp Asn Thr Ser Ser Leu Gly Pro Pro Ser Met
        915                 920                 925

Pro Val His Tyr Asp Ser Gln Leu Asp Thr Thr Leu Phe Gly Lys Lys
    930                 935                 940

Ser Ser Pro Leu Thr Glu Ser Gly Gly Pro Leu Ser Leu Ser Glu Glu
945                 950                 955                 960

Asn Asn Asp Ser Lys Leu Leu Glu Ser Gly Leu Met Asn Ser Gln Glu
                965                 970                 975

Ser Ser Trp Gly Lys Asn Val Ser Ser Thr Glu Ser Gly Arg Leu Phe
            980                 985                 990

Lys Gly Lys Arg Ala His Gly Pro  Ala Leu Leu Thr Lys  Asp Asn Ala
        995                 1000                1005

Leu Phe  Lys Val Ser Ile Ser  Leu Leu Lys Thr Asn  Lys Thr Ser
    1010                1015                1020

Asn Asn  Ser Ala Thr Asn Arg  Lys Thr His Ile Asp  Gly Pro Ser
    1025                1030                1035

Leu Leu  Ile Glu Asn Ser Pro  Ser Val Trp Gln Asn  Ile Leu Glu
```

-continued

```
    1040                1045                1050

Ser Asp  Thr Glu Phe Lys Lys  Val Thr Pro Leu Ile  His Asp Arg
    1055                1060                1065

Met Leu  Met Asp Lys Asn Ala  Thr Ala Leu Arg Leu  Asn His Met
    1070                1075                1080

Ser Asn  Lys Thr Thr Ser Ser  Lys Asn Met Glu Met  Val Gln Gln
    1085                1090                1095

Lys Lys  Glu Gly Pro Ile Pro  Pro Asp Ala Gln Asn  Pro Asp Met
    1100                1105                1110

Ser Phe  Phe Lys Met Leu Phe  Leu Pro Glu Ser Ala  Arg Trp Ile
    1115                1120                1125

Gln Arg  Thr His Gly Lys Asn  Ser Leu Asn Ser Gly  Gln Gly Pro
    1130                1135                1140

Ser Pro  Lys Gln Leu Val Ser  Leu Gly Pro Glu Lys  Ser Val Glu
    1145                1150                1155

Gly Gln  Asn Phe Leu Ser Glu  Lys Asn Lys Val Val  Val Gly Lys
    1160                1165                1170

Gly Glu  Phe Thr Lys Asp Val  Gly Leu Lys Glu Met  Val Phe Pro
    1175                1180                1185

Ser Ser  Arg Asn Leu Phe Leu  Thr Asn Leu Asp Asn  Leu His Glu
    1190                1195                1200

Asn Asn  Thr His Asn Gln Glu  Lys Lys Ile Gln Glu  Glu Ile Glu
    1205                1210                1215

Lys Lys  Glu Thr Leu Ile Gln  Glu Asn Val Val Leu  Pro Gln Ile
    1220                1225                1230

His Thr  Val Thr Gly Thr Lys  Asn Phe Met Lys Asn  Leu Phe Leu
    1235                1240                1245

Leu Ser  Thr Arg Gln Asn Val  Glu Gly Ser Tyr Asp  Gly Ala Tyr
    1250                1255                1260

Ala Pro  Val Leu Gln Asp Phe  Arg Ser Leu Asn Asp  Ser Thr Asn
    1265                1270                1275

Arg Thr  Lys Lys His Thr Ala  His Phe Ser Lys Lys  Gly Glu Glu
    1280                1285                1290

Glu Asn  Leu Glu Gly Leu Gly  Asn Gln Thr Lys Gln  Ile Val Glu
    1295                1300                1305

Lys Tyr  Ala Cys Thr Thr Arg  Ile Ser Pro Asn Thr  Ser Gln Gln
    1310                1315                1320

Asn Phe  Val Thr Gln Arg Ser  Lys Arg Ala Leu Lys  Gln Phe Arg
    1325                1330                1335

Leu Pro  Leu Glu Glu Thr Glu  Leu Glu Lys Arg Ile  Ile Val Asp
    1340                1345                1350

Asp Thr  Ser Thr Gln Trp Ser  Lys Asn Met Lys His  Leu Thr Pro
    1355                1360                1365

Ser Thr  Leu Thr Gln Ile Asp  Tyr Asn Glu Lys Glu  Lys Gly Ala
    1370                1375                1380

Ile Thr  Gln Ser Pro Leu Ser  Asp Cys Leu Thr Arg  Ser His Ser
    1385                1390                1395

Ile Pro  Gln Ala Asn Arg Ser  Pro Leu Pro Ile Ala  Lys Val Ser
    1400                1405                1410

Ser Phe  Pro Ser Ile Arg Pro  Ile Tyr Leu Thr Arg  Val Leu Phe
    1415                1420                1425
```

-continued

```
Gln Asp  Asn Ser Ser His Leu  Pro Ala Ala Ser Tyr  Arg Lys Lys
    1430                 1435                 1440

Asp Ser  Gly Val Gln Glu Ser  Ser His Phe Leu Gln  Gly Ala Lys
    1445                 1450                 1455

Lys Asn  Asn Leu Ser Leu Ala  Ile Leu Thr Leu Glu  Met Thr Gly
    1460                 1465                 1470

Asp Gln  Arg Glu Val Gly Ser  Leu Gly Thr Ser Ala  Thr Asn Ser
    1475                 1480                 1485

Val Thr  Tyr Lys Lys Val Glu  Asn Thr Val Leu Pro  Lys Pro Asp
    1490                 1495                 1500

Leu Pro  Lys Thr Ser Gly Lys  Val Glu Leu Leu Pro  Lys Val His
    1505                 1510                 1515

Ile Tyr  Gln Lys Asp Leu Phe  Pro Thr Glu Thr Ser  Asn Gly Ser
    1520                 1525                 1530

Pro Gly  His Leu Asp Leu Val  Glu Gly Ser Leu Leu  Gln Gly Thr
    1535                 1540                 1545

Glu Gly  Ala Ile Lys Trp Asn  Glu Ala Asn Arg Pro  Gly Lys Val
    1550                 1555                 1560

Pro Phe  Leu Arg Val Ala Thr  Glu Ser Ser Ala Lys  Thr Pro Ser
    1565                 1570                 1575

Lys Leu  Leu Asp Pro Leu Ala  Trp Asp Asn His Tyr  Gly Thr Gln
    1580                 1585                 1590

Ile Pro  Lys Glu Glu Trp Lys  Ser Gln Glu Lys Ser  Pro Glu Lys
    1595                 1600                 1605

Thr Ala  Phe Lys Lys Lys Asp  Thr Ile Leu Ser Leu  Asn Ala Cys
    1610                 1615                 1620

Glu Ser  Asn His Ala Ile Ala  Ala Ile Asn Glu Gly  Gln Asn Lys
    1625                 1630                 1635

Pro Glu  Ile Glu Val Thr Trp  Ala Lys Gln Gly Arg  Thr Glu Arg
    1640                 1645                 1650

Leu Cys  Ser Gln Asn Pro Pro  Val Leu Lys Arg His  Gln Arg Glu
    1655                 1660                 1665

Ile Thr  Arg Thr Thr Leu Gln  Ser Asp Gln Glu Glu  Ile Asp Tyr
    1670                 1675                 1680

Asp Asp  Thr Ile Ser Val Glu  Met Lys Lys Glu Asp  Phe Asp Ile
    1685                 1690                 1695

Tyr Asp  Glu Asp Glu Asn Gln  Ser Pro Arg Ser Phe  Gln Lys Lys
    1700                 1705                 1710

Thr Arg  His Tyr Phe Ile Ala  Ala Val Glu Arg Leu  Trp Asp Tyr
    1715                 1720                 1725

Gly Met  Ser Ser Ser Pro His  Val Leu Arg Asn Arg  Ala Gln Ser
    1730                 1735                 1740

Gly Ser  Val Pro Gln Phe Lys  Lys Val Val Phe Gln  Glu Phe Thr
    1745                 1750                 1755

Asp Gly  Ser Phe Thr Gln Pro  Leu Tyr Arg Gly Glu  Leu Asn Glu
    1760                 1765                 1770

His Leu  Gly Leu Leu Gly Pro  Tyr Ile Arg Ala Glu  Val Glu Asp
    1775                 1780                 1785

Asn Ile  Met Val Thr Phe Arg  Asn Gln Ala Ser Arg  Pro Tyr Ser
    1790                 1795                 1800
```

-continued

```
Phe Tyr  Ser Ser Leu Ile Ser  Tyr Glu Glu Asp Gln  Arg Gln Gly
    1805                 1810                 1815

Ala Glu  Pro Arg Lys Asn Phe  Val Lys Pro Asn Glu  Thr Lys Thr
    1820                 1825                 1830

Tyr Phe  Trp Lys Val Gln His  His Met Ala Pro Thr  Lys Asp Glu
    1835                 1840                 1845

Phe Asp  Cys Lys Ala Trp Ala  Tyr Phe Ser Asp Val  Asp Leu Glu
    1850                 1855                 1860

Lys Asp  Val His Ser Gly Leu  Ile Gly Pro Leu Leu  Val Cys His
    1865                 1870                 1875

Thr Asn  Thr Leu Asn Pro Ala  His Gly Arg Gln Val  Thr Val Gln
    1880                 1885                 1890

Glu Phe  Ala Leu Phe Phe Thr  Ile Phe Asp Glu Thr  Lys Ser Trp
    1895                 1900                 1905

Tyr Phe  Thr Glu Asn Met Glu  Arg Asn Cys Arg Ala  Pro Cys Asn
    1910                 1915                 1920

Ile Gln  Met Glu Asp Pro Thr  Phe Lys Glu Asn Tyr  Arg Phe His
    1925                 1930                 1935

Ala Ile  Asn Gly Tyr Ile Met  Asp Thr Leu Pro Gly  Leu Val Met
    1940                 1945                 1950

Ala Gln  Asp Gln Arg Ile Arg  Trp Tyr Leu Leu Ser  Met Gly Ser
    1955                 1960                 1965

Asn Glu  Asn Ile His Ser Ile  His Phe Ser Gly His  Val Phe Thr
    1970                 1975                 1980

Val Arg  Lys Lys Glu Glu Tyr  Lys Met Ala Leu Tyr  Asn Leu Tyr
    1985                 1990                 1995

Pro Gly  Val Phe Glu Thr Val  Glu Met Leu Pro Ser  Lys Ala Gly
    2000                 2005                 2010

Ile Trp  Arg Val Glu Cys Leu  Ile Gly Glu His Leu  His Ala Gly
    2015                 2020                 2025

Met Ser  Thr Leu Phe Leu Val  Tyr Ser Asn Lys Cys  Gln Thr Pro
    2030                 2035                 2040

Leu Gly  Met Ala Ser Gly His  Ile Arg Asp Phe Gln  Ile Thr Ala
    2045                 2050                 2055

Ser Gly  Gln Tyr Gly Gln Trp  Ala Pro Lys Leu Ala  Arg Leu His
    2060                 2065                 2070

Tyr Ser  Gly Ser Ile Asn Ala  Trp Ser Thr Lys Glu  Pro Phe Ser
    2075                 2080                 2085

Trp Ile  Lys Val Asp Leu Leu  Ala Pro Met Ile Ile  His Gly Ile
    2090                 2095                 2100

Lys Thr  Gln Gly Ala Arg Gln  Lys Phe Ser Ser Leu  Tyr Ile Ser
    2105                 2110                 2115

Gln Phe  Ile Ile Met Tyr Ser  Leu Asp Gly Lys Lys  Trp Gln Thr
    2120                 2125                 2130

Tyr Arg  Gly Asn Ser Thr Gly  Thr Leu Met Val Phe  Phe Gly Asn
    2135                 2140                 2145

Val Asp  Ser Ser Gly Ile Lys  His Asn Ile Phe Asn  Pro Pro Ile
    2150                 2155                 2160

Ile Ala  Arg Tyr Ile Arg Leu  His Pro Thr His Tyr  Ser Ile Arg
    2165                 2170                 2175

Ser Thr  Leu Arg Met Glu Leu  Met Gly Cys Asp Leu  Asn Ser Cys
```

-continued

```
    2180                2185                2190

Ser Met  Pro Leu Gly Met Glu  Ser Lys Ala Ile Ser  Asp Ala Gln
    2195                2200                2205

Ile Thr  Ala Ser Ser Tyr Phe  Thr Asn Met Phe Ala  Thr Trp Ser
    2210                2215                2220

Pro Ser  Lys Ala Arg Leu His  Leu Gln Gly Arg Ser  Asn Ala Trp
    2225                2230                2235

Arg Pro  Gln Val Asn Asn Pro  Lys Glu Trp Leu Gln  Val Asp Phe
    2240                2245                2250

Gln Lys  Thr Met Lys Val Thr  Gly Val Thr Thr Gln  Gly Val Lys
    2255                2260                2265

Ser Leu  Leu Thr Ser Met Tyr  Val Lys Glu Phe Leu  Ile Ser Ser
    2270                2275                2280

Ser Gln  Asp Gly His Gln Trp  Thr Leu Phe Phe Gln  Asn Gly Lys
    2285                2290                2295

Val Lys  Val Phe Gln Gly Asn  Gln Asp Ser Phe Thr  Pro Val Val
    2300                2305                2310

Asn Ser  Leu Asp Pro Pro Leu  Leu Thr Arg Tyr Leu  Arg Ile His
    2315                2320                2325

Pro Gln  Ser Trp Val His Gln  Ile Ala Leu Arg Met  Glu Val Leu
    2330                2335                2340

Gly Cys  Glu Ala Gln Asp Leu  Tyr
    2345                2350
```

<210> SEQ ID NO 20
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 20

```
atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc     60

accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg    120

ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac    180

acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc    240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac    300

gacaccgtgg tgatcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg    360

ggcgtgagct actggaaggc ctctgagggc gccgagtatg acgaccagac cagccagagg    420

gagaaggagg acgacaaggt gttccccggc ggcagccaca cctacgtgtg gcaggtgctg    480

aaggagaacg gccccatggc cagcgacccc ctgtgcctga cctacagcta cctgagccac    540

gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag    600

ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg    660

ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat    720

gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc    780

ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc    840

accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac    900
```

-continued

aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg 960

gacctgggcc agttcctgct gttctgccac atcagcagcc accagcacga cggcatggag 1020

gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag 1080

gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat 1140

gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc 1200

tgggtgcact acatcgccgc cgaggaggag gactgggact acgccccccct ggtgctggcc 1260

cccgacgaca ggagctacaa gagccagtac ctgaacaacg gcccccagag gatcggcagg 1320

aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc 1380

atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg 1440

ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctaccccca cggcatcacc 1500

gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc 1620

accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg 1680

gacctggcct ctggcctgat cggcccctg ctgatctgct acaaggagag cgtggaccag 1740

aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag 1800

aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg 1860

cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg 1920

ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc 2100

atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc 2160

atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg acatcagcgc ctacctgctg agcaagaaca acgccatcga gcccaggagc 2280

ttcagccaga accccccccgt gctgaagagg caccagaggg agatcaccag gaccaccctg 2340

cagagcgacc aggaggagat cgactatgat gacaccatca gcgtggagat gaagaaggag 2400

gacttcgaca tctacgacga ggacgagaac cagagcccca ggagcttcca gaagaagacc 2460

aggcactact tcatcgccgc cgtggagagg ctgtgggact atggcatgag cagcagcccc 2520

cacgtgctga ggaacagggc ccagagcggc agcgtgcccc agttcaagaa ggtggtgttc 2580

caggagttca ccgacggcag cttcacccag cccctgtaca gaggcgagct gaacgagcac 2640

ctgggcctgc tgggccccta catcagggcc gaggtggagg acaacatcat ggtgaccttc 2700

aggaaccagg ccagcaggcc ctacagcttc tacagcagcc tgatcagcta cgaggaggac 2760

cagaggcagg gcgccgagcc caggaagaac ttcgtgaagc ccaacgagac caagacctac 2820

ttctggaagg tgcagcacca catggccccc accaaggacg agttcgactg caaggcctgg 2880

gcctacttct ctgatgtgga cctggagaag gacgtgcaca gcggcctgat cggcccctg 2940

ctggtgtgcc acaccaacac cctgaacccc gcccacggca ggcaggtgac cgtgcaggag 3000

ttcgccctgt tcttcaccat cttcgacgag accaagagct ggtacttcac cgagaacatg 3060

gagaggaact gcagggcccc ctgcaacatc cagatggagg accccacctt caaggagaac 3120

tacaggttcc acgccatcaa cggctacatc atggacaccc tgcccggcct ggtgatggcc 3180

-continued

caggaccaga ggatcaggtg gtatctgctg agcatgggca gcaacgagaa catccacagc 3240

atccacttca gcggccacgt gttcaccgtg aggaagaagg aggagtacaa gatggccctg 3300

tacaacctgt accccggcgt gttcgagacc gtggagatgc tgcccagcaa ggccggcatc 3360

tggagggtgg agtgcctgat cggcgagcac ctgcacgccg gcatgagcac cctgttcctg 3420

gtgtacagca acaagtgcca gacccccctg ggcatggcca gcggccacat cagggacttc 3480

cagatcaccg cctctggcca gtacggccag tgggccccca agctggccag gctgcactac 3540

agcggcagca tcaacgcctg gagcaccaag gagcccttca gctggatcaa ggtggacctg 3600

ctggccccca tgatcatcca cggcatcaag acccagggcg ccaggcagaa gttcagcagc 3660

ctgtacatca gccagttcat catcatgtac agcctggacg gcaagaagtg gcagacctac 3720

aggggcaaca gcaccggcac cctgatggtg ttcttcggca acgtggacag cagcggcatc 3780

aagcacaaca tcttcaaccc ccccatcatc gccaggtaca tcaggctgca ccccacccac 3840

tacagcatca ggagcaccct gcggatggaa ctgatgggct gcgacctgaa cagctgcagc 3900

atgcccctgg gcatggagag caaggccatc tctgacgccc agatcaccgc cagcagctac 3960

ttcaccaaca tgttcgccac ctggagcccc agcaaggcca ggctgcacct gcagggcagg 4020

agcaacgcct ggaggcccca ggtgaacaac cccaaggagt ggctgcaggt ggacttccag 4080

aagaccatga aggtgaccgg cgtgaccacc cagggcgtga agagcctgct gaccagcatg 4140

tacgtgaagg agttcctgat cagcagcagc caggacggcc accagtggac cctgttcttc 4200

cagaacggca aagtgaaggt gttccagggc aaccaggaca gcttcacccc cgtggtgaac 4260

agcctggacc ccccccctgct gaccaggtat ctgaggatcc acccccagag ctgggtgcac 4320

cagatcgccc tgagaatgga agtgctggga tgcgaggccc aggacctgta ctga 4374

<210> SEQ ID NO 21
<211> LENGTH: 1457
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 21

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp

-continued

```
    130                 135                 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145                 150                 155                 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
                165                 170                 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
            180                 185                 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
        195                 200                 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
    210                 215                 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225                 230                 235                 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
                245                 250                 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
            260                 265                 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
        275                 280                 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
    290                 295                 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305                 310                 315                 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
                325                 330                 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
            340                 345                 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
                405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
                485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
    530                 535                 540
```

-continued

```
Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
                565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
                645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
            660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
        675                 680                 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
    690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705                 710                 715                 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
                725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
            740                 745                 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
        755                 760                 765

Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln
    770                 775                 780

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
785                 790                 795                 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
                805                 810                 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
            820                 825                 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
        835                 840                 845

Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
    850                 855                 860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His
865                 870                 875                 880

Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile
                885                 890                 895

Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser
            900                 905                 910

Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
        915                 920                 925

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val
    930                 935                 940
```

-continued

```
Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
945                 950                 955                 960

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu
                965                 970                 975

Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His
            980                 985                 990

Gly Arg Gln Val Thr Val Gln Glu  Phe Ala Leu Phe Phe  Thr Ile Phe
        995                 1000                1005

Asp Glu  Thr Lys Ser Trp Tyr  Phe Thr Glu Asn Met  Glu Arg Asn
    1010                1015                1020

Cys Arg  Ala Pro Cys Asn Ile  Gln Met Glu Asp Pro  Thr Phe Lys
    1025                1030                1035

Glu Asn  Tyr Arg Phe His Ala  Ile Asn Gly Tyr Ile  Met Asp Thr
    1040                1045                1050

Leu Pro  Gly Leu Val Met Ala  Gln Asp Gln Arg Ile  Arg Trp Tyr
    1055                1060                1065

Leu Leu  Ser Met Gly Ser Asn  Glu Asn Ile His Ser  Ile His Phe
    1070                1075                1080

Ser Gly  His Val Phe Thr Val  Arg Lys Lys Glu Glu  Tyr Lys Met
    1085                1090                1095

Ala Leu  Tyr Asn Leu Tyr Pro  Gly Val Phe Glu Thr  Val Glu Met
    1100                1105                1110

Leu Pro  Ser Lys Ala Gly Ile  Trp Arg Val Glu Cys  Leu Ile Gly
    1115                1120                1125

Glu His  Leu His Ala Gly Met  Ser Thr Leu Phe Leu  Val Tyr Ser
    1130                1135                1140

Asn Lys  Cys Gln Thr Pro Leu  Gly Met Ala Ser Gly  His Ile Arg
    1145                1150                1155

Asp Phe  Gln Ile Thr Ala Ser  Gly Gln Tyr Gly Gln  Trp Ala Pro
    1160                1165                1170

Lys Leu  Ala Arg Leu His Tyr  Ser Gly Ser Ile Asn  Ala Trp Ser
    1175                1180                1185

Thr Lys  Glu Pro Phe Ser Trp  Ile Lys Val Asp Leu  Leu Ala Pro
    1190                1195                1200

Met Ile  Ile His Gly Ile Lys  Thr Gln Gly Ala Arg  Gln Lys Phe
    1205                1210                1215

Ser Ser  Leu Tyr Ile Ser Gln  Phe Ile Ile Met Tyr  Ser Leu Asp
    1220                1225                1230

Gly Lys  Lys Trp Gln Thr Tyr  Arg Gly Asn Ser Thr  Gly Thr Leu
    1235                1240                1245

Met Val  Phe Phe Gly Asn Val  Asp Ser Ser Gly Ile  Lys His Asn
    1250                1255                1260

Ile Phe  Asn Pro Pro Ile Ile  Ala Arg Tyr Ile Arg  Leu His Pro
    1265                1270                1275

Thr His  Tyr Ser Ile Arg Ser  Thr Leu Arg Met Glu  Leu Met Gly
    1280                1285                1290

Cys Asp  Leu Asn Ser Cys Ser  Met Pro Leu Gly Met  Glu Ser Lys
    1295                1300                1305

Ala Ile  Ser Asp Ala Gln Ile  Thr Ala Ser Ser Tyr  Phe Thr Asn
    1310                1315                1320

Met Phe  Ala Thr Trp Ser Pro  Ser Lys Ala Arg Leu  His Leu Gln
```

-continued

```
    1325                1330                1335

Gly Arg  Ser Asn Ala Trp Arg  Pro Gln Val Asn Asn  Pro Lys Glu
    1340                1345                1350

Trp Leu  Gln Val Asp Phe Gln  Lys Thr Met Lys Val  Thr Gly Val
    1355                1360                1365

Thr Thr  Gln Gly Val Lys Ser  Leu Leu Thr Ser Met  Tyr Val Lys
    1370                1375                1380

Glu Phe  Leu Ile Ser Ser Ser  Gln Asp Gly His Gln  Trp Thr Leu
    1385                1390                1395

Phe Phe  Gln Asn Gly Lys Val  Lys Val Phe Gln Gly  Asn Gln Asp
    1400                1405                1410

Ser Phe  Thr Pro Val Val Asn  Ser Leu Asp Pro Pro  Leu Leu Thr
    1415                1420                1425

Arg Tyr  Leu Arg Ile His Pro  Gln Ser Trp Val His  Gln Ile Ala
    1430                1435                1440

Leu Arg  Met Glu Val Leu Gly  Cys Glu Ala Gln Asp  Leu Tyr
    1445                1450                1455


<210> SEQ ID NO 22
<211> LENGTH: 2220
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 22

gccaccagga gatactacct gggcgccgtg gagctgagct gggactacat gcagtctgac     60

ctgggcgagc tgcctgtgga cgccaggttc ccccccagag tgcccaagag cttccccttc    120

aacacctcag tggtgtacaa gaagaccctg ttcgtggagt tcaccgacca cctgttcaac    180

atcgccaagc ccaggccccc ctggatgggc ctgctgggcc ccaccatcca ggccgaggtg    240

tacgacaccg tggtgatcac cctgaagaac atggccagcc accccgtgag cctgcacgcc    300

gtgggcgtga gctactggaa ggcctctgag ggcgccgagt atgacgacca gaccagccag    360

agggagaagg aggacgacaa ggtgttcccc ggcggcagcc acacctacgt gtggcaggtg    420

ctgaaggaga acggccccat ggccagcgac cccctgtgcc tgacctacag ctacctgagc    480

cacgtggacc tggtgaagga cctgaactct ggcctgatcg gcgccctgct ggtgtgcagg    540

gagggcagcc tggccaagga gaagacccag accctgcaca agttcatcct gctgttcgcc    600

gtgttcgatg agggcaagag ctggcacagc gagaccaaga acagcctgat gcaggacagg    660

gatgccgcct ctgccagggc ctggcccaag atgcacaccg tgaacggcta cgtgaacagg    720

agcctgcccg gcctgatcgg ctgccacagg aagtctgtgt actggcacgt gatcggcatg    780

ggcaccaccc ccgaggtgca cagcatcttc ctggagggcc acaccttcct ggtgaggaac    840

cacaggcagg ccagcctgga gatcagcccc atcaccttcc tgaccgccca gaccctgctg    900

atggacctgg gccagttcct gctgttctgc cacatcagca gccaccagca cgacggcatg    960

gaggcctacg tgaaggtgga cagctgcccc gaggagcccc agctgaggat gaagaacaac   1020

gaggaggccg aggactatga tgatgacctg accgactctg agatggacgt ggtgaggttt   1080

gatgatgaca acagccccag cttcatccag atcaggtctg tggccaagaa gcaccccaag   1140

acctgggtgc actacatcgc cgccgaggag gaggactggg actacgcccc cctggtgctg   1200
```

-continued

gcccccgacg acaggagcta caagagccag tacctgaaca acggccccca gaggatcggc 1260

aggaagtaca agaaggtcag attcatggcc tacaccgacg agaccttcaa gaccagggag 1320

gccatccagc acgagtctgg catcctgggc cccctgctgt acggcgaggt gggcgacacc 1380

ctgctgatca tcttcaagaa ccaggccagc aggccctaca acatctaccc ccacggcatc 1440

accgatgtga ggcccctgta cagcaggagg ctgcccaagg gcgtgaagca cctgaaggac 1500

ttccccatcc tgcccggcga gatcttcaag tacaagtgga ccgtgaccgt ggaggatggc 1560

cccaccaagt ctgaccccag gtgcctgacc aggtactaca gcagcttcgt gaacatggag 1620

agggacctgg cctctggcct gatcggcccc ctgctgatct gctacaagga gagcgtggac 1680

cagaggggca accagatcat gtctgacaag aggaacgtga tcctgttctc tgtgttcgat 1740

gagaacagga gctggtatct gaccgagaac atccagaggt tcctgcccaa ccccgccggc 1800

gtgcagctgg aggaccccga gttccaggcc agcaacatca tgcacagcat caacggctac 1860

gtgttcgaca gcctgcagct gtctgtgtgc ctgcacgagg tggcctactg gtacatcctg 1920

agcatcggcg cccagaccga cttcctgtct gtgttcttct ctggctacac cttcaagcac 1980

aagatggtgt acgaggacac cctgaccctg ttcccccttca gcggcgagac cgtgttcatg 2040

agcatggaga accccggcct gtggatcctg ggctgccaca acagcgactt caggaacagg 2100

ggcatgaccg ccctgctgaa agtcagcagc tgcgacaaga acaccggcga ctactacgag 2160

gacagctacg aggacatcag cgcctacctg ctgagcaaga acaacgccat cgagcccagg 2220

<210> SEQ ID NO 23
<211> LENGTH: 2052
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 23

gagatcacca ggaccaccct gcagagcgac caggaggaga tcgactatga tgacaccatc 60

agcgtggaga tgaagaagga ggacttcgac atctacgacg aggacgagaa ccagagcccc 120

aggagcttcc agaagaagac caggcactac ttcatcgccg ccgtggagag gctgtgggac 180

tatggcatga gcagcagccc ccacgtgctg aggaacaggg cccagagcgg cagcgtgccc 240

cagttcaaga aggtggtgtt ccaggagttc accgacggca gcttcaccca gcccctgtac 300

agaggcgagc tgaacgagca cctgggcctg ctgggccccct acatcagggc cgaggtggag 360

gacaacatca tggtgacctt caggaaccag gccagcaggc cctacagctt ctacagcagc 420

ctgatcagct acgaggagga ccagaggcag ggcgccgagc ccaggaagaa cttcgtgaag 480

cccaacgaga ccaagaccta cttctggaag gtgcagcacc acatggcccc caccaaggac 540

gagttcgact gcaaggcctg ggcctacttc tctgatgtgg acctggagaa ggacgtgcac 600

agcggcctga tcggcccccct gctggtgtgc cacaccaaca ccctgaaccc cgcccacggc 660

aggcaggtga ccgtgcagga gttcgccctg ttcttcacca tcttcgacga gaccaagagc 720

tggtacttca ccgagaacat ggagaggaac tgcagggccc cctgcaacat ccagatggag 780

gaccccacct tcaaggagaa ctacaggttc cacgccatca acggctacat catggacacc 840

ctgcccggcc tggtgatggc ccaggaccag aggatcaggt ggtatctgct gagcatgggc 900

-continued

agcaacgaga acatccacag catccacttc agcggccacg tgttcaccgt gaggaagaag 960

gaggagtaca agatggccct gtacaacctg taccccggcg tgttcgagac cgtggagatg 1020

ctgcccagca aggccggcat ctggagggtg gagtgcctga tcggcgagca cctgcacgcc 1080

ggcatgagca ccctgttcct ggtgtacagc aacaagtgcc agacccccct gggcatggcc 1140

agcggccaca tcagggactt ccagatcacc gcctctggcc agtacggcca gtgggccccc 1200

aagctggcca ggctgcacta cagcggcagc atcaacgcct ggagcaccaa ggagcccttc 1260

agctggatca aggtggacct gctggccccc atgatcatcc acggcatcaa gacccagggc 1320

gccaggcaga agttcagcag cctgtacatc agccagttca tcatcatgta cagcctggac 1380

ggcaagaagt ggcagaccta caggggcaac agcaccggca ccctgatggt gttcttcggc 1440

aacgtggaca gcagcggcat caagcacaac atcttcaacc cccccatcat cgccaggtac 1500

atcaggctgc accccaccca ctacagcatc aggagcaccc tgcggatgga actgatgggc 1560

tgcgacctga acagctgcag catgcccctg ggcatggaga gcaaggccat ctctgacgcc 1620

cagatcaccg ccagcagcta cttcaccaac atgttcgcca cctggagccc cagcaaggcc 1680

aggctgcacc tgcagggcag gagcaacgcc tggaggcccc aggtgaacaa ccccaaggag 1740

tggctgcagg tggacttcca gaagaccatg aaggtgaccg gcgtgaccac ccagggcgtg 1800

aagagcctgc tgaccagcat gtacgtgaag gagttcctga tcagcagcag ccaggacggc 1860

caccagtgga ccctgttctt ccagaacggc aaagtgaagg tgttccaggg caaccaggac 1920

agcttcaccc ccgtggtgaa cagcctggac ccccccctgc tgaccaggta tctgaggatc 1980

caccccccaga gctgggtgca ccagatcgcc ctgagaatgg aagtgctggg atgcgaggcc 2040

caggacctgt ac 2052

<210> SEQ ID NO 24
<211> LENGTH: 2220
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 24

gccaccagga gatactacct gggggctgtg gaactttctt gggactacat gcagtctgac 60

ctgggagagc tgcctgtgga tgccaggttc ccacccagag tgcccaagtc cttcccattc 120

aacacctctg tggtctacaa gaagacactc tttgtggaat tcactgacca cctgttcaac 180

attgcaaaac ccagaccacc ctggatggga ctcctgggac ccaccattca ggctgaggtg 240

tatgacactg tggtcatcac cctcaagaac atggcatccc accctgtgtc tctgcatgct 300

gtgggagtct catactggaa agcctctgaa ggggctgagt atgatgacca gacatcccag 360

agagagaaag aggatgacaa ggtgttccct gggggatctc acacctatgt gtggcaagtc 420

ctcaaggaga atggacccat ggcatctgac ccactctgcc tgacatactc ctacctttct 480

catgtggacc tggtcaagga cctcaactct ggactgattg gggcactgct ggtgtgcagg 540

gaaggatccc tggccaagga gaaaacccag acactgcaca agttcattct cctgtttgct 600

gtctttgatg agggcaagtc ttggcactct gaaacaaaga actccctgat gcaagacagg 660

gatgctgcct ctgccagggc atggcccaag atgcacactg tgaatggcta tgtgaacaga 720

tcactgcctg gactcattgg ctgccacagg aaatctgtct actggcatgt gattggcatg 780

-continued

gggacaaccc ctgaagtgca ctccattttc ctggagggac acaccttcct ggtcaggaac 840

cacagacaag cctctctgga gatctctccc atcaccttcc tcactgcaca gacactgctg 900

atggaccttg gacagttcct gctgttctgc cacatctctt cccaccagca tgatggcatg 960

gaagcctatg tcaaggtgga ctcatgccct gaggaaccac agctcaggat gaagaacaat 1020

gaggaggctg aggactatga tgatgacctg actgactctg agatggatgt ggtcagattt 1080

gatgatgaca actctccatc cttcattcag atcaggtctg tggcaaagaa acaccccaag 1140

acatgggtgc actacattgc tgctgaggaa gaggactggg actatgcacc actggtcctg 1200

gcccctgatg acaggagcta caagtctcag tacctcaaca atggcccaca aagaattgga 1260

agaaagtaca agaaagtcag attcatggcc tacactgatg aaaccttcaa gacaagagaa 1320

gccattcagc atgagtctgg cattctggga ccactcctgt atggggaagt gggagacacc 1380

ctgctcatca tcttcaagaa ccaggcctcc aggccctaca acatctaccc acatggcatc 1440

actgatgtca ggcccctgta cagcaggaga ctgccaaaag gggtgaaaca cctcaaggac 1500

ttccccattc tgcctggaga gatcttcaag tacaagtgga ctgtcactgt ggaggatgga 1560

ccaacaaagt ctgaccccag gtgcctcacc agatactact cctcttttgt gaacatggag 1620

agagacctgg catctggact gattggacca ctgctcatct gctacaagga gtctgtggac 1680

cagagaggca accagatcat gtctgacaag agaaatgtga ttctgttctc tgtctttgat 1740

gagaacagat catggtacct gactgagaac attcagagat tcctgcccaa ccctgctggg 1800

gtgcaactgg aagaccctga gttccaggca agcaacatca tgcactccat caatggctat 1860

gtgtttgact ctctccagct ttctgtctgc ctgcatgagg tggcctactg gtacattctt 1920

tctattgggg cacaaactga cttccttttct gtcttcttct ctggatacac cttcaagcac 1980

aagatggtgt atgaggacac cctgacactc ttcccattct ctggggaaac tgtgttcatg 2040

agcatggaga accctggact gtggattctg ggatgccaca actctgactt cagaaacagg 2100

ggaatgactg cactgctcaa agtctcctcc tgtgacaaga acactgggga ctactatgag 2160

gactcttatg aggacatctc tgcctacctg ctcagcaaga acaatgccat tgagcccaga 2220

<210> SEQ ID NO 25
<211> LENGTH: 2052
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 25

gagatcacca ggacaaccct ccagtctgac caggaagaga ttgactatga tgacaccatt 60

tctgtggaga tgaagaagga ggactttgac atctatgatg aggacgagaa ccagtctcca 120

agatcattcc agaagaagac aagacactac ttcattgctg ctgtggaaag actgtgggac 180

tatggcatgt cttcctctcc ccatgtcctc aggaacaggg cacagtctgg ctctgtgcca 240

cagttcaaga aagtggtctt ccaggagttc actgatggct cattcaccca gcccctgtac 300

agaggggaac tgaatgagca cctgggactc ctgggaccat acatcagggc tgaggtggaa 360

gacaacatca tggtgacatt cagaaaccag gcctccaggc cctacagctt ctactcttcc 420

ctcatcagct atgaggaaga ccagagacaa ggggctgagc caagaaagaa ctttgtgaaa 480

-continued

cccaatgaaa ccaagaccta cttctggaaa gtccagcacc acatggcacc caccaaggat 540

gagtttgact gcaaggcctg ggcatacttc tctgatgtgg acctggagaa agatgtgcac 600

tctggcctga ttggcccact cctggtctgc cacaccaaca ccctgaaccc tgcacatgga 660

aggcaagtga ctgtgcagga gtttgccctc ttcttcacca tctttgatga aaccaagtca 720

tggtacttca ctgagaacat ggagagaaac tgcagagcac catgcaacat tcagatggaa 780

gaccccacct tcaaggagaa ctacaggttc catgccatca atggctacat catggacacc 840

ctgcctgggc ttgtcatggc acaggaccag agaatcagat ggtacctgct ttctatggga 900

tccaatgaga acattcactc catccacttc tctgggcatg tcttcactgt gagaaagaag 960

gaggaataca agatggccct gtacaacctc taccctgggg tctttgagac tgtggagatg 1020

ctgccctcca aagctggcat ctggagggtg gaatgcctca ttggggagca cctgcatgct 1080

ggcatgtcaa ccctgttcct ggtctacagc aacaagtgcc agacacccct gggaatggcc 1140

tctggccaca tcagggactt ccagatcact gcctctggcc agtatggcca gtgggcaccc 1200

aaactggcca ggctccacta ctctggctcc atcaatgcat ggtcaaccaa ggagccattc 1260

tcttggatca aggtggacct gctggcaccc atgatcattc atggcatcaa gacacagggg 1320

gcaagacaga aattctcctc tctgtacatc tcacagttca tcatcatgta ctctctggat 1380

ggcaagaagt ggcagacata cagaggcaac tccactggca ccctcatggt cttctttggc 1440

aatgtggaca gctctggcat caagcacaac atcttcaacc ctcccatcat tgccagatac 1500

atcaggctgc accccaccca ctactcaatc agatcaaccc tcaggatgga actgatggga 1560

tgtgacctga actcctgctc aatgcccctg ggaatggaga gcaaggccat ttctgatgcc 1620

cagatcactg catcctctta cttcaccaac atgtttgcca cctggtcacc atcaaaagcc 1680

aggctgcacc tccagggaag aagcaatgcc tggagacccc aggtcaacaa cccaaaggaa 1740

tggctgcaag tggacttcca gaagacaatg aaagtcactg gggtgacaac ccaggggtc 1800

aagtctctgc tcacctcaat gtatgtgaag gagttcctga tctcttcctc acaggatggc 1860

caccagtgga cactcttctt ccagaatggc aaagtcaagg tgttccaggg caaccaggac 1920

tctttcacac ctgtggtgaa ctcactggac ccccccctcc tgacaagata cctgagaatt 1980

caccccagt cttgggtcca ccagattgcc ctgagaatgg aagtcctggg atgtgaggca 2040

caagacctgt ac 2052

<210> SEQ ID NO 26
<211> LENGTH: 4332
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 26

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc 60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg 120

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

-continued

ggagtctcat actggaaagc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

gagaaagagg atgacaaggt gttccctggg ggatctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccatggc atctgaccca ctctgcctga catactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc cattttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gttctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccagagag 2280

atcaccagga caaccctcca gtctgaccag gaagagattg actatgatga caccatttct 2340

gtggagatga agaaggagga ctttgacatc tatgatgagg acgagaacca gtctccaaga 2400

tcattccaga agaagacaag acactacttc attgctgctg tggaaagact gtgggactat 2460

ggcatgtctt cctctcccca tgtcctcagg aacagggcac agtctggctc tgtgccacag 2520

ttcaagaaag tggtcttcca ggagttcact gatggctcat tcacccagcc cctgtacaga 2580

ggggaactga atgagcacct gggactcctg ggaccataca tcagggctga ggtggaagac 2640

-continued

aacatcatgg tgacattcag aaaccaggcc tccaggccct acagcttcta ctcttccctc 2700

atcagctatg aggaagacca gagacaaggg gctgagccaa gaaagaactt tgtgaaaccc 2760

aatgaaacca agacctactt ctggaaagtc cagcaccaca tggcacccac caaggatgag 2820

tttgactgca aggcctgggc atacttctct gatgtggacc tggagaaaga tgtgcactct 2880

ggcctgattg gcccactcct ggtctgccac accaacaccc tgaaccctgc acatggaagg 2940

caagtgactg tgcaggagtt tgccctcttc ttcaccatct ttgatgaaac caagtcatgg 3000

tacttcactg agaacatgga gagaaactgc agagcaccat gcaacattca gatggaagac 3060

cccaccttca aggagaacta caggttccat gccatcaatg gctacatcat ggacaccctg 3120

cctgggcttg tcatggcaca ggaccagaga atcagatggt acctgctttc tatgggatcc 3180

aatgagaaca ttcactccat ccacttctct gggcatgtct tcactgtgag aaagaaggag 3240

gaatacaaga tggccctgta caacctctac cctggggtct ttgagactgt ggagatgctg 3300

ccctccaaag ctggcatctg gagggtggaa tgcctcattg gggagcacct gcatgctggc 3360

atgtcaaccc tgttcctggt ctacagcaac aagtgccaga cacccctggg aatggcctct 3420

ggccacatca gggacttcca gatcactgcc tctggccagt atggccagtg ggcacccaaa 3480

ctggccaggc tccactactc tggctccatc aatgcatggt caaccaagga gccattctct 3540

tggatcaagg tggacctgct ggcacccatg atcattcatg gcatcaagac acaggggggca 3600

agacagaaat tctcctctct gtacatctca cagttcatca tcatgtactc tctggatggc 3660

aagaagtggc agacatacag aggcaactcc actggcaccc tcatggtctt ctttggcaat 3720

gtggacagct ctggcatcaa gcacaacatc ttcaaccctc ccatcattgc cagatacatc 3780

aggctgcacc ccacccacta ctcaatcaga tcaaccctca ggatggaact gatgggatgt 3840

gacctgaact cctgctcaat gcccctggga atggagagca aggccatttc tgatgcccag 3900

atcactgcat cctcttactt caccaacatg tttgccacct ggtcaccatc aaaagccagg 3960

ctgcacctcc agggaagaag caatgcctgg agaccccagg tcaacaaccc aaaggaatgg 4020

ctgcaagtgg acttccagaa gacaatgaaa gtcactgggg tgacaaccca gggggtcaag 4080

tctctgctca cctcaatgta tgtgaaggag ttcctgatct cttcctcaca ggatggccac 4140

cagtggacac tcttcttcca gaatggcaaa gtcaaggtgt tccagggcaa ccaggactct 4200

ttcacacctg tggtgaactc actggacccc cccctcctga caagatacct gagaattcac 4260

ccccagtctt gggtccacca gattgccctg agaatggaag tcctgggatg tgaggcacaa 4320

gacctgtact ga 4332

<210> SEQ ID NO 27
<211> LENGTH: 4368
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 27

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc 60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg 120

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

-continued

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

ggagtctcat actggaaagc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

gagaaagagg atgacaaggt gttccctggg ggatctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccatggc atctgaccca ctctgcctga catactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc cattttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gttctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccagaagc 2280

ttctctcaga attccagaca ccccagcacc agggagatca ccaggacaac cctccagtct 2340

gaccaggaag agattgacta tgatgacacc atttctgtgg agatgaagaa ggaggacttt 2400

gacatctatg atgaggacga gaaccagtct ccaagatcat tccagaagaa gacaagacac 2460

-continued

tacttcattg ctgctgtgga aagactgtgg gactatggca tgtcttcctc tccccatgtc 2520

ctcaggaaca gggcacagtc tggctctgtg ccacagttca agaaagtggt cttccaggag 2580

ttcactgatg gctcattcac ccagcccctg tacagagggg aactgaatga gcacctggga 2640

ctcctgggac catacatcag ggctgaggtg gaagacaaca tcatggtgac attcagaaac 2700

caggcctcca ggccctacag cttctactct tccctcatca gctatgagga agaccagaga 2760

caaggggctg agccaagaaa gaactttgtg aaacccaatg aaaccaagac ctacttctgg 2820

aaagtccagc accacatggc acccaccaag gatgagtttg actgcaaggc ctgggcatac 2880

ttctctgatg tggacctgga gaaagatgtg cactctggcc tgattggccc actcctggtc 2940

tgccacacca acaccctgaa ccctgcacat ggaaggcaag tgactgtgca ggagtttgcc 3000

ctcttcttca ccatctttga tgaaaccaag tcatggtact tcactgagaa catggagaga 3060

aactgcagag caccatgcaa cattcagatg gaagacccca ccttcaagga gaactacagg 3120

ttccatgcca tcaatggcta catcatggac accctgcctg ggcttgtcat ggcacaggac 3180

cagagaatca gatggtacct gctttctatg ggatccaatg agaacattca ctccatccac 3240

ttctctgggc atgtcttcac tgtgagaaag aaggaggaat acaagatggc cctgtacaac 3300

ctctaccctg gggtctttga gactgtggag atgctgccct ccaaagctgg catctggagg 3360

gtggaatgcc tcattgggga gcacctgcat gctggcatgt caaccctgtt cctggtctac 3420

agcaacaagt gccagacacc cctgggaatg gcctctggcc acatcaggga cttccagatc 3480

actgcctctg gccagtatgg ccagtgggca cccaaactgg ccaggctcca ctactctggc 3540

tccatcaatg catggtcaac caaggagcca ttctcttgga tcaaggtgga cctgctggca 3600

cccatgatca ttcatggcat caagacacag ggggcaagac agaaattctc ctctctgtac 3660

atctcacagt tcatcatcat gtactctctg gatggcaaga agtggcagac atacagaggc 3720

aactccactg gcaccctcat ggtcttcttt ggcaatgtgg acagctctgg catcaagcac 3780

aacatcttca accctcccat cattgccaga tacatcaggc tgcaccccac ccactactca 3840

atcagatcaa ccctcaggat ggaactgatg ggatgtgacc tgaactcctg ctcaatgccc 3900

ctgggaatgg agagcaaggc catttctgat gcccagatca ctgcatcctc ttacttcacc 3960

aacatgtttg ccacctggtc accatcaaaa gccaggctgc acctccaggg aagaagcaat 4020

gcctggagac cccaggtcaa caacccaaag gaatggctgc aagtggactt ccagaagaca 4080

atgaaagtca ctggggtgac aacccagggg gtcaagtctc tgctcacctc aatgtatgtg 4140

aaggagttcc tgatctcttc ctcacaggat ggccaccagt ggacactctt cttccagaat 4200

ggcaaagtca aggtgttcca gggcaaccag gactctttca cacctgtggt gaactcactg 4260

gacccccccc tcctgacaag atacctgaga attcaccccc agtcttgggt ccaccagatt 4320

gccctgagaa tggaagtcct gggatgtgag gcacaagacc tgtactga 4368

<210> SEQ ID NO 28
<211> LENGTH: 4332
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 28

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

-continued

accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg 120

ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac 180

acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc 240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac 300

gacaccgtgg tgatcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg 360

ggcgtgagct actggaaggc ctctgagggc gccgagtatg acgaccagac cagccagagg 420

gagaaggagg acgacaaggt gttccccggc ggcagccaca cctacgtgtg gcaggtgctg 480

aaggagaacg gccccatggc cagcgacccc ctgtgcctga cctacagcta cctgagccac 540

gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag 600

ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg 660

ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat 720

gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc 780

ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc 840

accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac 900

aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg 960

gacctgggcc agttcctgct gttctgccac atcagcagcc accagcacga cggcatggag 1020

gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag 1080

gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat 1140

gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc 1200

tgggtgcact acatcgccgc cgaggaggag gactgggact acgccccccct ggtgctggcc 1260

cccgacgaca ggagctacaa gagccagtac ctgaacaacg gcccccagag gatcggcagg 1320

aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc 1380

atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg 1440

ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctaccccca cggcatcacc 1500

gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc 1620

accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg 1680

gacctggcct ctggcctgat cggcccccctg ctgatctgct acaaggagag cgtggaccag 1740

aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag 1800

aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg 1860

cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg 1920

ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc 2100

atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc 2160

atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg acatcagcgc ctacctgctg agcaagaaca acgccatcga gcccagggag 2280

atcaccagga ccaccctgca gagcgaccag gaggagatcg actatgatga caccatcagc 2340

-continued

gtggagatga agaaggagga cttcgacatc tacgacgagg acgagaacca gagccccagg 2400

agcttccaga agaagaccag gcactacttc atcgccgccg tggagaggct gtgggactat 2460

ggcatgagca gcagccccca cgtgctgagg aacagggccc agagcggcag cgtgccccag 2520

ttcaagaagg tggtgttcca ggagttcacc gacggcagct tcacccagcc cctgtacaga 2580

ggcgagctga acgagcacct gggcctgctg ggcccctaca tcagggccga ggtggaggac 2640

aacatcatgg tgaccttcag gaaccaggcc agcaggccct acagcttcta cagcagcctg 2700

atcagctacg aggaggacca gaggcagggc gccgagccca ggaagaactt cgtgaagccc 2760

aacgagacca agacctactt ctggaaggtg cagcaccaca tggcccccac caaggacgag 2820

ttcgactgca aggcctgggc ctacttctct gatgtggacc tggagaagga cgtgcacagc 2880

ggcctgatcg gcccccctgct ggtgtgccac accaacaccc tgaaccccgc ccacggcagg 2940

caggtgaccg tgcaggagtt cgccctgttc ttcaccatct tcgacgagac caagagctgg 3000

tacttcaccg agaacatgga gaggaactgc agggcccccct gcaacatcca gatggaggac 3060

cccaccttca aggagaacta caggttccac gccatcaacg gctacatcat ggacaccctg 3120

cccggcctgg tgatggccca ggaccagagg atcaggtggt atctgctgag catgggcagc 3180

aacgagaaca tccacagcat ccacttcagc ggccacgtgt tcaccgtgag gaagaaggag 3240

gagtacaaga tggccctgta caacctgtac cccggcgtgt tcgagaccgt ggagatgctg 3300

cccagcaagg ccggcatctg gagggtggag tgcctgatcg gcgagcacct gcacgccggc 3360

atgagcaccc tgttcctggt gtacagcaac aagtgccaga ccccctgggg catggccagc 3420

ggccacatca gggacttcca gatcaccgcc tctggccagt acggccagtg ggcccccaag 3480

ctggccaggc tgcactacag cggcagcatc aacgcctgga gcaccaagga gcccttcagc 3540

tggatcaagg tggacctgct ggcccccatg atcatccacg gcatcaagac ccagggcgcc 3600

aggcagaagt tcagcagcct gtacatcagc cagttcatca tcatgtacag cctggacggc 3660

aagaagtggc agacctacag gggcaacagc accggcaccc tgatggtgtt cttcggcaac 3720

gtggacagca gcggcatcaa gcacaacatc ttcaaccccc ccatcatcgc caggtacatc 3780

aggctgcacc ccacccacta cagcatcagg agcaccctgc ggatggaact gatgggctgc 3840

gacctgaaca gctgcagcat gcccctgggc atggagagca aggccatctc tgacgcccag 3900

atcaccgcca gcagctactt caccaacatg ttcgccacct ggagccccag caaggccagg 3960

ctgcacctgc agggcaggag caacgcctgg aggccccagg tgaacaaccc caaggagtgg 4020

ctgcaggtgg acttccagaa gaccatgaag gtgaccggcg tgaccaccca gggcgtgaag 4080

agcctgctga ccagcatgta cgtgaaggag ttcctgatca gcagcagcca ggacggccac 4140

cagtggaccc tgttcttcca gaacggcaaa gtgaaggtgt tccagggcaa ccaggacagc 4200

ttcacccccg tggtgaacag cctggacccc cccctgctga ccaggtatct gaggatccac 4260

ccccagagct gggtgcacca gatcgccctg agaatggaag tgctgggatg cgaggcccag 4320

gacctgtact ga 4332

<210> SEQ ID NO 29
<211> LENGTH: 4368
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

polynucleotide

<400> SEQUENCE: 29

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg 120

ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac 180

acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc 240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac 300

gacaccgtgg tgatcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg 360

ggcgtgagct actggaaggc ctctgagggc gccgagtatg acgaccagac cagccagagg 420

gagaaggagg acgacaaggt gttccccggc ggcagccaca cctacgtgtg gcaggtgctg 480

aaggagaacg gccccatggc cagcgacccc ctgtgcctga cctacagcta cctgagccac 540

gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag 600

ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg 660

ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat 720

gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc 780

ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc 840

accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac 900

aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg 960

gacctgggcc agttcctgct gttctgccac atcagcagcc accagcacga cggcatggag 1020

gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag 1080

gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat 1140

gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc 1200

tgggtgcact acatcgccgc cgaggaggag gactgggact acgcccccct ggtgctggcc 1260

cccgacgaca ggagctacaa gagccagtac ctgaacaacg gcccccagag gatcggcagg 1320

aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc 1380

atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg 1440

ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctaccccca cggcatcacc 1500

gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc 1620

accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg 1680

gacctggcct ctggcctgat cggcccccctg ctgatctgct acaaggagag cgtggaccag 1740

aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag 1800

aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg 1860

cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg 1920

ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc 2100

atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc 2160

-continued

atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg acatcagcgc ctacctgctg agcaagaaca acgccatcga gcccaggagc 2280

ttcagccaga actccagaca ccccagcacc agggagatca ccaggaccac cctgcagagc 2340

gaccaggagg agatcgacta tgatgacacc atcagcgtgg agatgaagaa ggaggacttc 2400

gacatctacg acgaggacga gaaccagagc cccaggagct tccagaagaa gaccaggcac 2460

tacttcatcg ccgccgtgga gaggctgtgg gactatggca tgagcagcag cccccacgtg 2520

ctgaggaaca gggcccagag cggcagcgtg ccccagttca agaaggtggt gttccaggag 2580

ttcaccgacg gcagcttcac ccagcccctg tacagaggcg agctgaacga gcacctgggc 2640

ctgctgggcc cctacatcag ggccgaggtg gaggacaaca tcatggtgac cttcaggaac 2700

caggccagca ggccctacag cttctacagc agcctgatca gctacgagga ggaccagagg 2760

cagggcgccg agcccaggaa gaacttcgtg aagcccaacg agaccaagac ctacttctgg 2820

aaggtgcagc accacatggc ccccaccaag gacgagttcg actgcaaggc ctgggcctac 2880

ttctctgatg tggacctgga gaaggacgtg cacagcggcc tgatcggccc cctgctggtg 2940

tgccacacca acaccctgaa ccccgcccac ggcaggcagg tgaccgtgca ggagttcgcc 3000

ctgttcttca ccatcttcga cgagaccaag agctggtact tcaccgagaa catggagagg 3060

aactgcaggg ccccctgcaa catccagatg gaggacccca ccttcaagga gaactacagg 3120

ttccacgcca tcaacggcta catcatggac accctgcccg gcctggtgat ggcccaggac 3180

cagaggatca ggtggtatct gctgagcatg ggcagcaacg agaacatcca cagcatccac 3240

ttcagcggcc acgtgttcac cgtgaggaag aaggaggagt acaagatggc cctgtacaac 3300

ctgtaccccg gcgtgttcga gaccgtggag atgctgccca gcaaggccgg catctggagg 3360

gtggagtgcc tgatcggcga gcacctgcac gccggcatga gcaccctgtt cctggtgtac 3420

agcaacaagt gccagacccc cctgggcatg gccagcggcc acatcaggga cttccagatc 3480

accgcctctg gccagtacgg ccagtgggcc cccaagctgg ccaggctgca ctacagcggc 3540

agcatcaacg cctggagcac caaggagccc ttcagctgga tcaaggtgga cctgctggcc 3600

cccatgatca tccacggcat caagacccag ggcgccaggc agaagttcag cagcctgtac 3660

atcagccagt tcatcatcat gtacagcctg gacggcaaga agtggcagac ctacaggggc 3720

aacagcaccg gcaccctgat ggtgttcttc ggcaacgtgg acagcagcgg catcaagcac 3780

aacatcttca acccccccat catcgccagg tacatcaggc tgcaccccac ccactacagc 3840

atcaggagca ccctgcggat ggaactgatg ggctgcgacc tgaacagctg cagcatgccc 3900

ctgggcatgg agagcaaggc catctctgac gcccagatca ccgccagcag ctacttcacc 3960

aacatgttcg ccacctggag ccccagcaag gccaggctgc acctgcaggg caggagcaac 4020

gcctggaggc cccaggtgaa caaccccaag gagtggctgc aggtggactt ccagaagacc 4080

atgaaggtga ccggcgtgac cacccagggc gtgaagagcc tgctgaccag catgtacgtg 4140

aaggagttcc tgatcagcag cagccaggac ggccaccagt ggaccctgtt cttccagaac 4200

ggcaaagtga aggtgttcca gggcaaccag gacagcttca cccccgtggt gaacagcctg 4260

gacccccccc tgctgaccag gtatctgagg atccaccccc agagctgggt gcaccagatc 4320

gccctgagaa tggaagtgct gggatgcgag gcccaggacc tgtactga 4368

<210> SEQ ID NO 30

-continued

<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 30

Ser Phe Ser Gln Asn Pro Pro Val Leu Lys Arg His Gln Arg
1 5 10

<210> SEQ ID NO 31
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Sus sp.

<400> SEQUENCE: 31

Ser Phe Ala Gln Asn Ser Arg Pro Pro Ser Ala Ser Ala Pro Lys Pro
1 5 10 15

Pro Val Leu Arg Arg His Gln Arg
20

<210> SEQ ID NO 32
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Sus sp.

<400> SEQUENCE: 32

Ser Phe Ser Gln Asn Ser Arg His Gln Ala Tyr Arg Tyr Arg Arg Gly
1 5 10 15

<210> SEQ ID NO 33
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 33

Thr Thr Tyr Val Asn Arg Ser Leu
1 5

<210> SEQ ID NO 34
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Pro Gln Leu Arg Met Lys Asn
1 5

<210> SEQ ID NO 35
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 35

Val Asp Gln Arg Gly Asn Gln
1 5

-continued

<210> SEQ ID NO 36
<211> LENGTH: 87
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 36

agcttcagcc agaatgtgag caacaatgtg agcaacaatg ccaccaataa tgctaccaac 60

ccacctgtcc tgaaacgcca ccagagg 87

<210> SEQ ID NO 37
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 37

agcttcagcc agaatgtgag caacaatgcc accaacaatg tgagcaaccc acctgtcctg 60

aaacgccacc agagg 75

<210> SEQ ID NO 38
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 38

agcttcagcc agaatgtgag caataatgcc accaacccac ctgtcctgaa acgccaccag 60

agg 63

<210> SEQ ID NO 39
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 39

agcttcagcc agaatgtgag caataatcca cctgtcctga aacgccacca gagg 54

<210> SEQ ID NO 40
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 40

agcttcagcc agaataggag cctgccacct gtcctgaaac gccaccagag g 51

<210> SEQ ID NO 41
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 41

agcttcagcc agaatgccac taatgtgtct aacaactctg ctacctctgc tgactctgct 60

gtgagcccac ctgtcctgaa acgccaccag agg 93

<210> SEQ ID NO 42
<211> LENGTH: 69
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 42

agcttcagcc agaatgccac caactatgtg aacaggagcc tgccacctgt cctgaaacgc 60

caccagagg 69

<210> SEQ ID NO 43
<211> LENGTH: 105
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 43

agcttcagcc agaatgccac caactatgtg aacaggagcc tgtctgccac ctctgctgac 60

tctgctgtga gccagaatcc acctgtcctg aaacgccacc agagg 105

<210> SEQ ID NO 44
<211> LENGTH: 84
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 44

agcttcagcc agaatgtgag caacaatgtg agcaatgctg tgtctgctgt gtctgctcca 60

cctgtcctga aacgccacca gagg 84

<210> SEQ ID NO 45
<211> LENGTH: 90
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 45

agcttcagcc agaatatcac tgtggcctct gccacctcta acatcactgt ggcctctgct 60

gacccacctg tcctgaaacg ccaccagagg 90

<210> SEQ ID NO 46
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 46

agcttcagcc agaatatcac tgtgaccaac atcactgtga ctgccccacc tgtcctgaaa 60

cgccaccaga gg 72

<210> SEQ ID NO 47
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 47

agcttcagcc agaatcagac tgtgaccaac atcactgtga ctgccccacc tgtcctgaaa 60

cgccaccaga gg 72

<210> SEQ ID NO 48
<211> LENGTH: 93
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide

<400> SEQUENCE: 48

agcttcagcc agaatgccac taatgtgtct aacaacagca acaccagcaa tgacagcaat 60

gtgtctccac ctgtcctgaa acgccaccag agg 93

<210> SEQ ID NO 49
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 49

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc 60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg 120

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

ggagtctcat actggaaagc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

gagaaagagg atgacaaggt gttccctggg ggatctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccatggc atctgaccca ctctgcctga catactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

-continued

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc cattttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gtcctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccagaagc 2280

ttctctcaga atccacctgt cctgaagaga caccagagag agatcaccag gacaaccctc 2340

cagtctgacc aggaagagat tgactatgat gacaccattt ctgtggagat gaagaaggag 2400

gactttgaca tctatgatga ggacgagaac cagtctccaa gatcattcca gaagaagaca 2460

agacactact tcattgctgc tgtggaaaga ctgtgggact atggcatgtc ttcctctccc 2520

catgtcctca ggaacagggc acagtctggc tctgtgccac agttcaagaa agtggtcttc 2580

caggagttca ctgatggctc attcacccag cccctgtaca gaggggaact gaatgagcac 2640

ctgggactcc tgggaccata catcagggct gaggtggaag acaacatcat ggtgacattc 2700

agaaaccagg cctccaggcc ctacagcttc tactcttccc tcatcagcta tgaggaagac 2760

cagagacaag gggctgagcc aagaaagaac tttgtgaaac ccaatgaaac caagacctac 2820

ttctggaaag tccagcacca catggcaccc accaaggatg agtttgactg caaggcctgg 2880

gcatacttct ctgatgtgga cctggagaaa gatgtgcact ctggcctgat tggcccactc 2940

ctggtctgcc acaccaacac cctgaaccct gcacatggaa ggcaagtgac tgtgcaggag 3000

tttgccctct tcttcaccat ctttgatgaa accaagtcat ggtacttcac tgagaacatg 3060

-continued

gagagaaact gcagagcacc atgcaacatt cagatggaag accccacctt caaggagaac 3120

tacaggttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggca 3180

caggaccaga gaatcagatg gtacctgctt tctatgggat ccaatgagaa cattcactcc 3240

atccacttct ctgggcatgt cttcactgtg agaaagaagg aggaatacaa gatggccctg 3300

tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc 3360

tggagggtgg aatgcctcat tggggagcac ctgcatgctg gcatgtcaac cctgttcctg 3420

gtctacagca acaagtgcca gacacccctg ggaatggcct ctggccacat cagggacttc 3480

cagatcactg cctctggcca gtatggccag tgggcaccca aactggccag gctccactac 3540

tctggctcca tcaatgcatg gtcaaccaag gagccattct cttggatcaa ggtggacctg 3600

ctggcaccca tgatcattca tggcatcaag acacaggggg caagacagaa attctcctct 3660

ctgtacatct cacagttcat catcatgtac tctctggatg gcaagaagtg gcagacatac 3720

agaggcaact ccactggcac cctcatggtc ttctttggca atgtggacag ctctggcatc 3780

aagcacaaca tcttcaaccc tcccatcatt gccagataca tcaggctgca ccccacccac 3840

tactcaatca gatcaaccct caggatggaa ctgatgggat gtgacctgaa ctcctgctca 3900

atgcccctgg gaatggagag caaggccatt tctgatgccc agatcactgc atcctcttac 3960

ttcaccaaca tgtttgccac ctggtcacca tcaaaagcca ggctgcacct ccagggaaga 4020

agcaatgcct ggagacccca ggtcaacaac ccaaaggaat ggctgcaagt ggacttccag 4080

aagacaatga aagtcactgg ggtgacaacc caggggtca agtctctgct cacctcaatg 4140

tatgtgaagg agttcctgat ctcttcctca caggatggcc accagtggac actcttcttc 4200

cagaatggca aagtcaaggt gttccagggc aaccaggact ctttcacacc tgtggtgaac 4260

tcactggacc ccccctcct gacaagatac ctgagaattc acccccagtc ttgggtccac 4320

cagattgccc tgagaatgga agtcctggga tgtgaggcac aagacctgta ctga 4374

<210> SEQ ID NO 50
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(45)

<400> SEQUENCE: 50

gtg agc aac aat gtg agc aac aat gcc acc aat aat gct acc aac 45
Val Ser Asn Asn Val Ser Asn Asn Ala Thr Asn Asn Ala Thr Asn
1 5 10 15

<210> SEQ ID NO 51
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 51

Val Ser Asn Asn Val Ser Asn Asn Ala Thr Asn Asn Ala Thr Asn
1 5 10 15

-continued

<210> SEQ ID NO 52
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(33)

<400> SEQUENCE: 52

gtg agc aac aat gcc acc aac aat gtg agc aac 33
Val Ser Asn Asn Ala Thr Asn Asn Val Ser Asn
1 5 10

<210> SEQ ID NO 53
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 53

Val Ser Asn Asn Ala Thr Asn Asn Val Ser Asn
1 5 10

<210> SEQ ID NO 54
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(21)

<400> SEQUENCE: 54

gtg agc aat aat gcc acc aac 21
Val Ser Asn Asn Ala Thr Asn
1 5

<210> SEQ ID NO 55
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 55

Val Ser Asn Asn Ala Thr Asn
1 5

<210> SEQ ID NO 56
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(12)

-continued

<400> SEQUENCE: 56

gtg agc aat aat 12
Val Ser Asn Asn
1

<210> SEQ ID NO 57
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 57

Val Ser Asn Asn
1

<210> SEQ ID NO 58
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(9)

<400> SEQUENCE: 58

agg agc ctg 9
Arg Ser Leu
1

<210> SEQ ID NO 59
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 59

Arg Ser Leu
1

<210> SEQ ID NO 60
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(51)

<400> SEQUENCE: 60

gcc act aat gtg tct aac aac tct gct acc tct gct gac tct gct gtg 48
Ala Thr Asn Val Ser Asn Asn Ser Ala Thr Ser Ala Asp Ser Ala Val
1 5 10 15

agc 51
Ser

<210> SEQ ID NO 61
<211> LENGTH: 17
<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 61

Ala Thr Asn Val Ser Asn Asn Ser Ala Thr Ser Ala Asp Ser Ala Val
1 5 10 15

Ser

<210> SEQ ID NO 62
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(27)

<400> SEQUENCE: 62

gcc acc aac tat gtg aac agg agc ctg 27
Ala Thr Asn Tyr Val Asn Arg Ser Leu
1 5

<210> SEQ ID NO 63
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 63

Ala Thr Asn Tyr Val Asn Arg Ser Leu
1 5

<210> SEQ ID NO 64
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(63)

<400> SEQUENCE: 64

gcc acc aac tat gtg aac agg agc ctg tct gcc acc tct gct gac tct 48
Ala Thr Asn Tyr Val Asn Arg Ser Leu Ser Ala Thr Ser Ala Asp Ser
1 5 10 15

gct gtg agc cag aat 63
Ala Val Ser Gln Asn
20

<210> SEQ ID NO 65
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 65

-continued

Ala Thr Asn Tyr Val Asn Arg Ser Leu Ser Ala Thr Ser Ala Asp Ser
1 5 10 15

Ala Val Ser Gln Asn
20

<210> SEQ ID NO 66
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(42)

<400> SEQUENCE: 66

gtg agc aac aat gtg agc aat gct gtg tct gct gtg tct gct 42
Val Ser Asn Asn Val Ser Asn Ala Val Ser Ala Val Ser Ala
1 5 10

<210> SEQ ID NO 67
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 67

Val Ser Asn Asn Val Ser Asn Ala Val Ser Ala Val Ser Ala
1 5 10

<210> SEQ ID NO 68
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(48)

<400> SEQUENCE: 68

atc act gtg gcc tct gcc acc tct aac atc act gtg gcc tct gct gac 48
Ile Thr Val Ala Ser Ala Thr Ser Asn Ile Thr Val Ala Ser Ala Asp
1 5 10 15

<210> SEQ ID NO 69
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 69

Ile Thr Val Ala Ser Ala Thr Ser Asn Ile Thr Val Ala Ser Ala Asp
1 5 10 15

<210> SEQ ID NO 70
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(30)

<400> SEQUENCE: 70

atc act gtg acc aac atc act gtg act gcc 30
Ile Thr Val Thr Asn Ile Thr Val Thr Ala
1 5 10

<210> SEQ ID NO 71
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 71

Ile Thr Val Thr Asn Ile Thr Val Thr Ala
1 5 10

<210> SEQ ID NO 72
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(30)

<400> SEQUENCE: 72

cag act gtg acc aac atc act gtg act gcc 30
Gln Thr Val Thr Asn Ile Thr Val Thr Ala
1 5 10

<210> SEQ ID NO 73
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 73

Gln Thr Val Thr Asn Ile Thr Val Thr Ala
1 5 10

<210> SEQ ID NO 74
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1)..(51)

<400> SEQUENCE: 74

gcc act aat gtg tct aac aac agc aac acc agc aat gac agc aat gtg 48
Ala Thr Asn Val Ser Asn Asn Ser Asn Thr Ser Asn Asp Ser Asn Val
1 5 10 15

-continued

tct 51
Ser

<210> SEQ ID NO 75
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 75

Ala Thr Asn Val Ser Asn Asn Ser Asn Thr Ser Asn Asp Ser Asn Val
1 5 10 15

Ser

<210> SEQ ID NO 76
<211> LENGTH: 405
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Met Pro Leu Leu Leu Tyr Thr Cys Leu Leu Trp Leu Pro Thr Ser Gly
1 5 10 15

Leu Trp Thr Val Gln Ala Met Asp Pro Asn Ala Ala Tyr Val Asn Met
20 25 30

Ser Asn His His Arg Gly Leu Ala Ser Ala Asn Val Asp Phe Ala Phe
35 40 45

Ser Leu Tyr Lys His Leu Val Ala Leu Ser Pro Lys Lys Asn Ile Phe
50 55 60

Ile Ser Pro Val Ser Ile Ser Met Ala Leu Ala Met Leu Ser Leu Gly
65 70 75 80

Thr Cys Gly His Thr Arg Ala Gln Leu Leu Gln Gly Leu Gly Phe Asn
85 90 95

Leu Thr Glu Arg Ser Glu Thr Glu Ile His Gln Gly Phe Gln His Leu
100 105 110

His Gln Leu Phe Ala Lys Ser Asp Thr Ser Leu Glu Met Thr Met Gly
115 120 125

Asn Ala Leu Phe Leu Asp Gly Ser Leu Glu Leu Leu Glu Ser Phe Ser
130 135 140

Ala Asp Ile Lys His Tyr Tyr Glu Ser Glu Val Leu Ala Met Asn Phe
145 150 155 160

Gln Asp Trp Ala Thr Ala Ser Arg Gln Ile Asn Ser Tyr Val Lys Asn
165 170 175

Lys Thr Gln Gly Lys Ile Val Asp Leu Phe Ser Gly Leu Asp Ser Pro
180 185 190

Ala Ile Leu Val Leu Val Asn Tyr Ile Phe Phe Lys Gly Thr Trp Thr
195 200 205

Gln Pro Phe Asp Leu Ala Ser Thr Arg Glu Glu Asn Phe Tyr Val Asp
210 215 220

Glu Thr Thr Val Val Lys Val Pro Met Met Leu Gln Ser Ser Thr Ile
225 230 235 240

Ser Tyr Leu His Asp Ser Glu Leu Pro Cys Gln Leu Val Gln Met Asn
245 250 255

Tyr Val Gly Asn Gly Thr Val Phe Phe Ile Leu Pro Asp Lys Gly Lys

-continued

```
           260                 265                 270

Met Asn Thr Val Ile Ala Ala Leu Ser Arg Asp Thr Ile Asn Arg Trp
        275                 280                 285

Ser Ala Gly Leu Thr Ser Ser Gln Val Asp Leu Tyr Ile Pro Lys Val
    290                 295                 300

Thr Ile Ser Gly Val Tyr Asp Leu Gly Asp Val Leu Glu Glu Met Gly
305                 310                 315                 320

Ile Ala Asp Leu Phe Thr Asn Gln Ala Asn Phe Ser Arg Ile Thr Gln
                325                 330                 335

Asp Ala Gln Leu Lys Ser Ser Lys Val Val His Lys Ala Val Leu Gln
            340                 345                 350

Leu Asn Glu Glu Gly Val Asp Thr Ala Gly Ser Thr Gly Val Thr Leu
        355                 360                 365

Asn Leu Thr Ser Lys Pro Ile Ile Leu Arg Phe Asn Gln Pro Phe Ile
    370                 375                 380

Ile Met Ile Phe Asp His Phe Thr Trp Ser Ser Leu Phe Leu Ala Arg
385                 390                 395                 400

Val Met Asn Pro Val
                405


<210> SEQ ID NO 77
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Asn Met Ser Asn
1


<210> SEQ ID NO 78
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Asn Leu Thr Glu
1


<210> SEQ ID NO 79
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Asn Lys Thr Gln
1


<210> SEQ ID NO 80
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Asn Gly Thr Val
1


<210> SEQ ID NO 81
<211> LENGTH: 4
```

-continued

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Asn Phe Ser Arg
1

<210> SEQ ID NO 82
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

Asn Leu Thr Ser
1

<210> SEQ ID NO 83
<211> LENGTH: 41
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 83

Leu Ser Lys Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Ala
1 5 10 15

Thr Asn Val Ser Asn Asn Ser Asn Thr Ser Asn Asp Ser Asn Val Ser
20 25 30

Pro Pro Val Leu Lys Arg His Gln Arg
35 40

<210> SEQ ID NO 84
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 84

Asn Ala Thr Asn
1

<210> SEQ ID NO 85
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 85

Asn Val Ser Asn
1

<210> SEQ ID NO 86
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

-continued

<400> SEQUENCE: 86

Asn Asn Ser Asn
1

<210> SEQ ID NO 87
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 87

Asn Thr Ser Asn
1

<210> SEQ ID NO 88
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 88

Asn Asp Ser Asn
1

<210> SEQ ID NO 89
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 89

Asn Val Ser Pro
1

<210> SEQ ID NO 90
<211> LENGTH: 4377
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 90

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc 60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg 120

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

ggagtctcat actggaaagc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

gagaaagagg atgacaaggt gttccctggg ggatctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccatggc atctgaccca ctctgcctga catactccta cctttctcat 540

-continued

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc cattttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gtcctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca ataccaccta cgtgaaccgc 2280

tccctgtctc agaatccacc tgtcctgaag agacaccaga gagagatcac caggacaacc 2340

ctccagtctg accaggaaga gattgactat gatgacacca tttctgtgga gatgaagaag 2400

gaggactttg acatctatga tgaggacgag aaccagtctc caagatcatt ccagaagaag 2460

acaagacact acttcattgc tgctgtggaa agactgtggg actatggcat gtcttcctct 2520

ccccatgtcc tcaggaacag ggcacagtct ggctctgtgc cacagttcaa gaaagtggtc 2580

ttccaggagt tcactgatgg ctcattcacc cagcccctgt acagagggga actgaatgag 2640

cacctgggac tcctgggacc atacatcagg gctgaggtgg aagacaacat catggtgaca 2700

ttcagaaacc aggcctccag gccctacagc ttctactctt ccctcatcag ctatgaggaa 2760

gaccagagac aaggggctga gccaagaaag aactttgtga aacccaatga aaccaagacc 2820

-continued

tacttctgga aagtccagca ccacatggca cccaccaagg atgagtttga ctgcaaggcc 2880

tgggcatact tctctgatgt ggacctggag aaagatgtgc actctggcct gattggccca 2940

ctcctggtct gccacaccaa caccctgaac cctgcacatg gaaggcaagt gactgtgcag 3000

gagtttgccc tcttcttcac catctttgat gaaaccaagt catggtactt cactgagaac 3060

atggagagaa actgcagagc accatgcaac attcagatgg aagaccccac cttcaaggag 3120

aactacaggt tccatgccat caatggctac atcatggaca ccctgcctgg gcttgtcatg 3180

gcacaggacc agagaatcag atggtacctg ctttctatgg gatccaatga gaacattcac 3240

tccatccact tctctgggca tgtcttcact gtgagaaaga aggaggaata caagatggcc 3300

ctgtacaacc tctaccctgg ggtctttgag actgtggaga tgctgccctc caaagctggc 3360

atctggaggg tggaatgcct cattggggag cacctgcatg ctggcatgtc aaccctgttc 3420

ctggtctaca gcaacaagtg ccagacaccc ctgggaatgg cctctggcca catcagggac 3480

ttccagatca ctgcctctgg ccagtatggc cagtgggcac ccaaactggc caggctccac 3540

tactctggct ccatcaatgc atggtcaacc aaggagccat tctcttggat caaggtggac 3600

ctgctggcac ccatgatcat tcatggcatc aagacacagg gggcaagaca gaaattctcc 3660

tctctgtaca tctcacagtt catcatcatg tactctctgg atggcaagaa gtggcagaca 3720

tacagaggca actccactgg caccctcatg gtcttctttg gcaatgtgga cagctctggc 3780

atcaagcaca acatcttcaa ccctcccatc attgccagat acatcaggct gcaccccacc 3840

cactactcaa tcagatcaac cctcaggatg gaactgatgg gatgtgacct gaactcctgc 3900

tcaatgcccc tgggaatgga gagcaaggcc atttctgatg cccagatcac tgcatcctct 3960

tacttcacca acatgtttgc cacctggtca ccatcaaaag ccaggctgca cctccaggga 4020

agaagcaatg cctggagacc ccaggtcaac aacccaaagg aatggctgca agtggacttc 4080

cagaagacaa tgaaagtcac tggggtgaca acccaggggg tcaagtctct gctcacctca 4140

atgtatgtga aggagttcct gatctcttcc tcacaggatg gccaccagtg gacactcttc 4200

ttccagaatg gcaaagtcaa ggtgttccag ggcaaccagg actctttcac acctgtggtg 4260

aactcactgg acccccccct cctgacaaga tacctgagaa ttcaccccca gtcttgggtc 4320

caccagattg ccctgagaat ggaagtcctg ggatgtgagg cacaagacct gtactga 4377

<210> SEQ ID NO 91
<211> LENGTH: 4377
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 91

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc 60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg 120

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcgtcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

ggagtctcat actggaaatc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

-continued

gagaaagagg atgacaaggt gttccctggg aagtctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccactgc atctgaccca ccctgcctga catactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc cattttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gttctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca ataccaccta cgtgaaccgc 2280

tccctgtctc agaatccacc tgtcctgaag agacaccaga gagagatcac caggacaacc 2340

ctccagtctg accaggaaga gattgactat gatgacacca tttctgtgga gatgaagaag 2400

gaggactttg acatctatga tgaggacgag aaccagtctc caagatcatt ccagaagaag 2460

acaagacact acttcattgc tgctgtggaa agactgtggg actatggcat gtcttcctct 2520

ccccatgtcc tcaggaacag ggcacagtct ggctctgtgc cacagttcaa gaaagtggtc 2580

ttccaggagt tcactgatgg ctcattcacc cagcccctgt acagagggga actgaatgag 2640

cacctgggac tcctgggacc atacatcagg gctgaggtgg aagacaacat catggtgaca 2700

-continued

ttcagaaacc aggcctccag gccctacagc ttctactctt ccctcatcag ctatgaggaa 2760

gaccagagac aaggggctga gccaagaaag aactttgtga aacccaatga aaccaagacc 2820

tacttctgga aagtccagca ccacatggca cccaccaagg atgagtttga ctgcaaggcc 2880

tgggcatact tctctgatgt ggacctggag aaagatgtgc actctggcct gattggccca 2940

ctcctggtct gccacaccaa caccctgaac cctgcacatg gaaggcaagt gactgtgcag 3000

gagtttgccc tcttcttcac catctttgat gaaaccaagt catggtactt cactgagaac 3060

atggagagaa actgcagagc accatgcaac attcagatgg aagaccccac cttcaaggag 3120

aactacaggt tccatgccat caatggctac atcatggaca ccctgcctgg gcttgtcatg 3180

gcacaggacc agagaatcag atggtacctg ctttctatgg gatccaatga gaacattcac 3240

tccatccact tctctgggca tgtcttcact gtgagaaaga aggaggaata caagatggcc 3300

ctgtacaacc tctaccctgg ggtctttgag actgtggaga tgctgccctc caaagctggc 3360

atctggaggg tggaatgcct cattggggag cacctgcatg ctggcatgtc aaccctgttc 3420

ctggtctaca gcaacaagtg ccagacaccc ctgggaatgg cctctggcca catcagggac 3480

ttccagatca ctgcctctgg ccagtatggc cagtgggcac ccaaactggc caggctccac 3540

tactctggct ccatcaatgc atggtcaacc aaggagccat tctcttggat caaggtggac 3600

ctgctggcac ccatgatcat tcatggcatc aagacacagg gggcaagaca gaaattctcc 3660

tctctgtaca tctcacagtt catcatcatg tactctctgg atggcaagaa gtggcagaca 3720

tacagaggca actccactgg caccctcatg gtcttctttg gcaatgtgga cagctctggc 3780

atcaagcaca acatcttcaa ccctcccatc attgccagat acatcaggct gcaccccacc 3840

cactactcaa tcagatcaac cctcaggatg gaactgatgg gatgtgacct gaactcctgc 3900

tcaatgcccc tgggaatgga gagcaaggcc atttctgatg cccagatcac tgcatcctct 3960

tacttcacca acatgtttgc cacctggtca ccatcaaaag ccaggctgca cctccaggga 4020

agaagcaatg cctggagacc ccaggtcaac aacccaaagg aatggctgca agtggacttc 4080

cagaagacaa tgaaagtcac tggggtgaca acccaggggg tcaagtctct gctcacctca 4140

atgtatgtga aggagttcct gatctcttcc tcacaggatg gccaccagtg gacactcttc 4200

ttccagaatg gcaaagtcaa ggtgttccag ggcaaccagg actctttcac acctgtggtg 4260

aactcactgg acccccccct cctgacaaga tacctgagaa ttcaccccca gtcttgggtc 4320

caccagattg ccctgagaat ggaagtcctg ggatgtgagg cacaagacct gtactga 4377

<210> SEQ ID NO 92
<211> LENGTH: 4377
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 92

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc 60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg 120

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

-continued

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

ggagtctcat actggaaagc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

gagaaagagg atgacaaggt gttccctggg ggatctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccatggc atctgaccca ctctgcctga catactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc cattttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gttctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca ataccaccta cgtgaaccgc 2280

tccctgtctc agaatccacc tgtcctgaag agacaccaga gagagatcac caggacaacc 2340

ctccagtctg accaggaaga gattgactat gatgacacca tttctgtgga gatgaagaag 2400

gaggactttg acatctatga tgaggacgag aaccagtctc caagatcatt ccagaagaag 2460

acaagacact acttcattgc tgctgtggaa agactgtggg actatggcat gtcttcctct 2520

-continued

ccccatgtcc tcaggaacag ggcacagtct ggctctgtgc cacagttcaa gaaagtggtc 2580

ttccaggagt tcactgatgg ctcattcacc cagcccctgt acagagggga actgaatgag 2640

cacctgggac tcctgggacc atacatcagg gctgaggtgg aagacaacat catggtgaca 2700

ttcagaaacc aggcctccag gccctacagc ttctactctt ccctcatcag ctatgaggaa 2760

gaccagagac aaggggctga gccaagaaag aactttgtga aacccaatga aaccaagacc 2820

tacttctgga aagtccagca ccacatggca cccaccaagg atgagtttga ctgcaaggcc 2880

tgggcatact tctctgatgt ggacctggag aaagatgtgc actctggcct gattggccca 2940

ctcctggtct gccacaccaa caccctgaac cctgcacatg gaaggcaagt gactgtgcag 3000

gagtttgccc tcttcttcac catctttgat gaaaccaagt catggtactt cactgagaac 3060

atggagagaa actgcagagc accatgcaac attcagatgg aagaccccac cttcaaggag 3120

aactacaggt tccatgccat caatggctac atcatggaca ccctgcctgg gcttgtcatg 3180

gcacaggacc agagaatcag atggtacctg ctttctatgg gatccaatga gaacattcac 3240

tccatccact tctctgggca tgtcttcact gtgagaaaga aggaggaata caagatggcc 3300

ctgtacaacc tctaccctgg ggtctttgag actgtggaga tgctgccctc caaagctggc 3360

atctggaggg tggaatgcct cattggggag cacctgcatg ctggcatgtc aaccctgttc 3420

ctggtctaca gcaacaagtg ccagacaccc ctgggaatgg cctctggcca catcagggac 3480

ttccagatca ctgcctctgg ccagtatggc cagtgggcac ccaaactggc caggctccac 3540

tactctggct ccatcaatgc atggtcaacc aaggagccat tctcttggat caaggtggac 3600

ctgctggcac ccatgatcat tcatggcatc aagacacagg gggcaagaca gaaattctcc 3660

tctctgtaca tctcacagtt catcatcatg tactctctgg atggcaagaa gtggcagaca 3720

tacagaggca actccactgg caccctcatg gtcttctttg gcaatgtgga cagctctggc 3780

atcaagcaca acatcttcaa ccctcccatc attgccagat acatcaggct gcaccccacc 3840

cactactcaa tcagatcaac cctcaggatg gaactgatgg gatgtgacct gaactcctgc 3900

tcaatgcccc tgggaatgga gagcaaggcc atttctgatg cccagatcac tgcatcctct 3960

tacttcacca acatgtttgc cacctggtca ccatcaaaag ccaggctgca cctccaggga 4020

agaagcaatg cctggagacc ccaggtcaac aacccaaagg aatggctgca agtggacttc 4080

cagaagacaa tgaaagtcac tggggtgaca acccaggggg tcaagtctct gctcacctca 4140

atgtatgtga aggagttcct gatctcttcc tcacaggatg gccaccagtg gacactcttc 4200

ttccagaatg gcaaagtcaa ggtgttccag ggcaaccagg actctttcac acctgtggtg 4260

aactcactgg acccccccct cctgacaaga tacctgagaa ttcaccccca gtcttgggtc 4320

caccagattg ccctgagaat ggaagtcctg ggatgtgagg cacaagacct gtactga 4377

<210> SEQ ID NO 93
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 93

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc 60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg 120

-continued

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcgtcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

ggagtctcat actggaaatc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

gagaaagagg atgacaaggt gttccctggg aagtctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccactgc atctgaccca ccctgcctga catactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc cattttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gttctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccagaagc 2280

ttctctcaga atccacctgt cctgaagaga caccagagag agatcaccag gacaaccctc 2340

cagtctgacc aggaagagat tgactatgat gacaccattt ctgtggagat gaagaaggag 2400

-continued

gactttgaca tctatgatga ggacgagaac cagtctccaa gatcattcca gaagaagaca 2460

agacactact tcattgctgc tgtggaaaga ctgtgggact atggcatgtc ttcctctccc 2520

catgtcctca ggaacagggc acagtctggc tctgtgccac agttcaagaa agtggtcttc 2580

caggagttca ctgatggctc attcacccag cccctgtaca gaggggaact gaatgagcac 2640

ctgggactcc tgggaccata catcagggct gaggtggaag acaacatcat ggtgacattc 2700

agaaaccagg cctccaggcc ctacagcttc tactcttccc tcatcagcta tgaggaagac 2760

cagagacaag gggctgagcc aagaaagaac tttgtgaaac ccaatgaaac caagacctac 2820

ttctggaaag tccagcacca catggcaccc accaaggatg agtttgactg caaggcctgg 2880

gcatacttct ctgatgtgga cctggagaaa gatgtgcact ctggcctgat tggcccactc 2940

ctggtctgcc acaccaacac cctgaaccct gcacatggaa ggcaagtgac tgtgcaggag 3000

tttgccctct tcttcaccat ctttgatgaa accaagtcat ggtacttcac tgagaacatg 3060

gagagaaact gcagagcacc atgcaacatt cagatggaag accccacctt caaggagaac 3120

tacaggttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggca 3180

caggaccaga gaatcagatg gtacctgctt tctatgggat ccaatgagaa cattcactcc 3240

atccacttct ctgggcatgt cttcactgtg agaaagaagg aggaatacaa gatggccctg 3300

tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc 3360

tggagggtgg aatgcctcat tggggagcac ctgcatgctg gcatgtcaac cctgttcctg 3420

gtctacagca acaagtgcca gacacccctg ggaatggcct ctggccacat cagggacttc 3480

cagatcactg cctctggcca gtatggccag tgggcaccca aactggccag gctccactac 3540

tctggctcca tcaatgcatg gtcaaccaag gagccattct cttggatcaa ggtggacctg 3600

ctggcaccca tgatcattca tggcatcaag acacaggggg caagacagaa attctcctct 3660

ctgtacatct cacagttcat catcatgtac tctctggatg gcaagaagtg gcagacatac 3720

agaggcaact ccactggcac cctcatggtc ttctttggca atgtggacag ctctggcatc 3780

aagcacaaca tcttcaaccc tcccatcatt gccagataca tcaggctgca ccccacccac 3840

tactcaatca gatcaaccct caggatggaa ctgatgggat gtgacctgaa ctcctgctca 3900

atgcccctgg gaatggagag caaggccatt tctgatgccc agatcactgc atcctcttac 3960

ttcaccaaca tgtttgccac ctggtcacca tcaaaagcca ggctgcacct ccagggaaga 4020

agcaatgcct ggagacccca ggtcaacaac ccaaaggaat ggctgcaagt ggacttccag 4080

aagacaatga aagtcactgg ggtgacaacc caggggtca agtctctgct cacctcaatg 4140

tatgtgaagg agttcctgat ctcttcctca caggatggcc accagtggac actcttcttc 4200

cagaatggca aagtcaaggt gttccagggc aaccaggact ctttcacacc tgtggtgaac 4260

tcactggacc ccccctcct gacaagatac ctgagaattc acccccagtc ttgggtccac 4320

cagattgccc tgagaatgga agtcctggga tgtgaggcac aagacctgta ctga 4374

<210> SEQ ID NO 94
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

-continued

<400> SEQUENCE: 94

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcgtcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaagtc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg aagagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccactgc ctctgaccca ccctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gttctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

-continued

agctatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccaggagc 2280

ttcagccaga atccacctgt cctgaaacgc caccagaggg agatcaccag gaccaccctc 2340

cagtctgacc aggaggagat tgactatgat gacaccattt ctgtggagat gaagaaagag 2400

gactttgaca tctatgacga ggacgagaac cagagcccaa ggagcttcca gaagaagacc 2460

aggcactact tcattgctgc tgtggagcgc ctgtgggact atggcatgag ctccagcccc 2520

catgtcctca ggaacagggc ccagtctggc tctgtgccac agttcaagaa agtggtcttc 2580

caagagttca ctgatggcag cttcacccag cccctgtaca gaggggagct gaatgagcac 2640

ctgggactcc tgggcccata catcagggct gaggtggagg acaacatcat ggtgaccttc 2700

cgcaaccagg cctccaggcc ctacagcttc tacagctccc tcatcagcta tgaggaggac 2760

cagaggcagg gggctgagcc acgcaagaac tttgtgaaac ccaatgaaac caagacctac 2820

ttctggaaag tccagcacca catggccccc accaaggatg agtttgactg caaggcctgg 2880

gcctacttct ctgatgtgga cctggagaag gatgtgcact ctggcctgat tggcccactc 2940

ctggtctgcc acaccaacac cctgaaccct gcccatggaa ggcaagtgac tgtgcaggag 3000

tttgccctct tcttcaccat ctttgatgaa accaagagct ggtacttcac tgagaacatg 3060

gagcgcaact gcagggcccc atgcaacatt cagatggagg accccacctt caaagagaac 3120

taccgcttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggcc 3180

caggaccaga ggatcaggtg gtacctgctt tctatgggct ccaatgagaa cattcactcc 3240

atccacttct ctgggcatgt cttcactgtg cgcaagaagg aggagtacaa gatggccctg 3300

tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc 3360

tggagggtgg agtgcctcat tggggagcac ctgcatgctg gcatgagcac cctgttcctg 3420

gtctacagca acaagtgcca gacccccctg ggaatggcct ctggccacat cagggacttc 3480

cagatcactg cctctggcca gtatggccag tgggccccca agctggccag gctccactac 3540

tctggatcca tcaatgcctg gagcaccaag gagccattca gctggatcaa agtggacctg 3600

ctggccccca tgatcatcca tggcatcaag acccaggggg ccaggcagaa gttctccagc 3660

ctgtacatca gccagttcat catcatgtac agcctggatg gcaagaaatg gcagacctac 3720

agaggcaact ccactggaac actcatggtc ttctttggca atgtggacag ctctggcatc 3780

aagcacaaca tcttcaaccc cccaatcatc gccagataca tcaggctgca ccccacccac 3840

tacagcatcc gcagcaccct caggatggag ctgatgggct gtgacctgaa ctcctgcagc 3900

atgcccctgg gcatggagag caaggccatt tctgatgccc agatcactgc ctccagctac 3960

ttcaccaaca tgtttgccac ctggagccca agcaaggcca ggctgcacct ccagggaagg 4020

agcaatgcct ggaggcccca ggtcaacaac ccaaaggagt ggctgcaggt ggacttccag 4080

aagaccatga aggtcactgg ggtgaccacc caggggggtca agagcctgct caccagcatg 4140

tatgtgaagg agttcctgat cagctccagc caggatggcc accagtggac cctcttcttc 4200

cagaatggca aggtcaaggt gttccagggc aaccaggaca gcttcacccc tgtggtgaac 4260

agcctggacc ccccccctcct gaccagatac ctgaggattc acccccagag ctgggtccac 4320

cagattgccc tgaggatgga ggtcctggga tgtgaggccc aggacctgta ctga 4374

<210> SEQ ID NO 95
<211> LENGTH: 4377
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 95

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaaggc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg ggcagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccatggc ctctgaccca ctctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gttctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

-continued

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

agctatgagg acatctctgc ctacctgctc agcaagaaca ataccaccta cgtgaaccgc 2280

tccctgagcc agaatccacc tgtcctgaaa cgccaccaga gggagatcac caggaccacc 2340

ctccagtctg accaggagga gattgactat gatgacacca tttctgtgga gatgaagaaa 2400

gaggactttg acatctatga cgaggacgag aaccagagcc caaggagctt ccagaagaag 2460

accaggcact acttcattgc tgctgtggag cgcctgtggg actatggcat gagctccagc 2520

ccccatgtcc tcaggaacag ggcccagtct ggctctgtgc cacagttcaa gaaagtggtc 2580

ttccaagagt tcactgatgg cagcttcacc cagcccctgt acagagggga gctgaatgag 2640

cacctgggac tcctgggccc atacatcagg gctgaggtgg aggacaacat catggtgacc 2700

ttccgcaacc aggcctccag gccctacagc ttctacagct ccctcatcag ctatgaggag 2760

gaccagaggc agggggctga gccacgcaag aactttgtga aacccaatga aaccaagacc 2820

tacttctgga aagtccagca ccacatggcc cccaccaagg atgagtttga ctgcaaggcc 2880

tgggcctact tctctgatgt ggacctggag aaggatgtgc actctggcct gattggccca 2940

ctcctggtct gccacaccaa caccctgaac cctgcccatg gaaggcaagt gactgtgcag 3000

gagtttgccc tcttcttcac catctttgat gaaaccaaga gctggtactt cactgagaac 3060

atggagcgca actgcagggc cccatgcaac attcagatgg aggaccccac cttcaaagag 3120

aactaccgct tccatgccat caatggctac atcatggaca ccctgcctgg gcttgtcatg 3180

gcccaggacc agaggatcag gtggtacctg ctttctatgg gctccaatga gaacattcac 3240

tccatccact tctctgggca tgtcttcact gtgcgcaaga aggaggagta caagatggcc 3300

ctgtacaacc tctaccctgg ggtctttgag actgtggaga tgctgccctc caaagctggc 3360

atctggaggg tggagtgcct cattggggag cacctgcatg ctggcatgag caccctgttc 3420

ctggtctaca gcaacaagtg ccagaccccc ctgggaatgg cctctggcca catcagggac 3480

ttccagatca ctgcctctgg ccagtatggc cagtgggccc ccaagctggc caggctccac 3540

tactctggat ccatcaatgc ctggagcacc aaggagccat tcagctggat caaagtggac 3600

ctgctggccc ccatgatcat ccatggcatc aagacccagg gggccaggca gaagttctcc 3660

agcctgtaca tcagccagtt catcatcatg tacagcctgg atggcaagaa atggcagacc 3720

tacagaggca actccactgg aacactcatg gtcttctttg gcaatgtgga cagctctggc 3780

atcaagcaca acatcttcaa ccccccaatc atcgccagat acatcaggct gcaccccacc 3840

cactacagca tccgcagcac cctcaggatg gagctgatgg gctgtgacct gaactcctgc 3900

agcatgcccc tgggcatgga gagcaaggcc atttctgatg cccagatcac tgcctccagc 3960

tacttcacca acatgtttgc cacctggagc ccaagcaagg ccaggctgca cctccaggga 4020

aggagcaatg cctggaggcc ccaggtcaac aacccaaagg agtggctgca ggtggacttc 4080

cagaagacca tgaaggtcac tggggtgacc acccaggggg tcaagagcct gctcaccagc 4140

atgtatgtga aggagttcct gatcagctcc agccaggatg gccaccagtg gaccctcttc 4200

ttccagaatg gcaaggtcaa ggtgttccag ggcaaccagg acagcttcac ccctgtggtg 4260

aacagcctgg acccccccct cctgaccaga tacctgagga ttcaccccca gagctgggtc 4320

caccagattg ccctgaggat ggaggtcctg ggatgtgagg cccaggacct gtactga 4377

-continued

<210> SEQ ID NO 96
<211> LENGTH: 4377
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 96

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcgtcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaagtc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg aagagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccactgc ctctgaccca ccctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gttctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

-continued

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

agctatgagg acatctctgc ctacctgctc agcaagaaca ataccaccta cgtgaaccgc 2280

tccctgagcc agaatccacc tgtcctgaaa cgccaccaga gggagatcac caggaccacc 2340

ctccagtctg accaggagga gattgactat gatgacacca tttctgtgga gatgaagaaa 2400

gaggactttg acatctatga cgaggacgag aaccagagcc caaggagctt ccagaagaag 2460

accaggcact acttcattgc tgctgtggag cgcctgtggg actatggcat gagctccagc 2520

ccccatgtcc tcaggaacag ggcccagtct ggctctgtgc cacagttcaa gaaagtggtc 2580

ttccaagagt tcactgatgg cagcttcacc cagcccctgt acagagggga gctgaatgag 2640

cacctgggac tcctgggccc atacatcagg gctgaggtgg aggacaacat catggtgacc 2700

ttccgcaacc aggcctccag gccctacagc ttctacagct ccctcatcag ctatgaggag 2760

gaccagaggc agggggctga gccacgcaag aactttgtga aacccaatga aaccaagacc 2820

tacttctgga aagtccagca ccacatggcc cccaccaagg atgagtttga ctgcaaggcc 2880

tgggcctact tctctgatgt ggacctggag aaggatgtgc actctggcct gattggccca 2940

ctcctggtct gccacaccaa caccctgaac cctgcccatg gaaggcaagt gactgtgcag 3000

gagtttgccc tcttcttcac catctttgat gaaaccaaga gctggtactt cactgagaac 3060

atggagcgca actgcagggc cccatgcaac attcagatgg aggaccccac cttcaaagag 3120

aactaccgct tccatgccat caatggctac atcatggaca ccctgcctgg gcttgtcatg 3180

gcccaggacc agaggatcag gtggtacctg ctttctatgg gctccaatga gaacattcac 3240

tccatccact tctctgggca tgtcttcact gtgcgcaaga aggaggagta caagatggcc 3300

ctgtacaacc tctaccctgg ggtctttgag actgtggaga tgctgccctc caaagctggc 3360

atctggaggg tggagtgcct cattggggag cacctgcatg ctggcatgag caccctgttc 3420

ctggtctaca gcaacaagtg ccagaccccc ctgggaatgg cctctggcca catcagggac 3480

ttccagatca ctgcctctgg ccagtatggc cagtgggccc ccaagctggc caggctccac 3540

tactctggat ccatcaatgc ctggagcacc aaggagccat tcagctggat caaagtggac 3600

ctgctggccc ccatgatcat ccatggcatc aagacccagg gggccaggca gaagttctcc 3660

agcctgtaca tcagccagtt catcatcatg tacagcctgg atggcaagaa atggcagacc 3720

tacagaggca actccactgg aacactcatg gtcttctttg gcaatgtgga cagctctggc 3780

atcaagcaca acatcttcaa ccccccaatc atcgccagat acatcaggct gcaccccacc 3840

cactacagca tccgcagcac cctcaggatg gagctgatgg gctgtgacct gaactcctgc 3900

agcatgcccc tgggcatgga gagcaaggcc atttctgatg cccagatcac tgcctccagc 3960

tacttcacca acatgtttgc cacctggagc ccaagcaagg ccaggctgca cctccaggga 4020

aggagcaatg cctggaggcc ccaggtcaac aacccaaagg agtggctgca ggtggacttc 4080

cagaagacca tgaaggtcac tggggtgacc acccaggggg tcaagagcct gctcaccagc 4140

atgtatgtga aggagttcct gatcagctcc agccaggatg gccaccagtg gaccctcttc 4200

-continued

ttccagaatg gcaaggtcaa ggtgttccag ggcaaccagg acagcttcac ccctgtggtg 4260

aacagcctgg acccccccct cctgaccaga tacctgagga ttcaccccca gagctgggtc 4320

caccagattg ccctgaggat ggaggtcctg ggatgtgagg cccaggacct gtactga 4377

<210> SEQ ID NO 97
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 97

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaaggc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg ggcagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccatggc ctctgaccca ctctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gtcctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

-continued

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

agctatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccaggagc 2280

ttcagccaga atccacctgt cctgaaacgc caccagaggg agatcaccag gaccaccctc 2340

cagtctgacc aggaggagat tgactatgat gacaccattt ctgtggagat gaagaaagag 2400

gactttgaca tctatgacga ggacgagaac cagagcccaa ggagcttcca gaagaagacc 2460

aggcactact tcattgctgc tgtggagcgc ctgtgggact atggcatgag ctccagcccc 2520

catgtcctca ggaacagggc ccagtctggc tctgtgccac agttcaagaa agtggtcttc 2580

caagagttca ctgatggcag cttcacccag cccctgtaca gaggggagct gaatgagcac 2640

ctgggactcc tgggcccata catcagggct gaggtggagg acaacatcat ggtgaccttc 2700

cgcaaccagg cctccaggcc ctacagcttc tacagctccc tcatcagcta tgaggaggac 2760

cagaggcagg gggctgagcc acgcaagaac tttgtgaaac ccaatgaaac caagacctac 2820

ttctggaaag tccagcacca catggccccc accaaggatg agtttgactg caaggcctgg 2880

gcctacttct ctgatgtgga cctggagaag gatgtgcact ctggcctgat tggcccactc 2940

ctggtctgcc acaccaacac cctgaaccct gcccatggaa ggcaagtgac tgtgcaggag 3000

tttgccctct tcttcaccat ctttgatgaa accaagagct ggtacttcac tgagaacatg 3060

gagcgcaact gcagggcccc atgcaacatt cagatggagg accccacctt caaagagaac 3120

taccgcttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggcc 3180

caggaccaga ggatcaggtg gtacctgctt tctatgggct ccaatgagaa cattcactcc 3240

atccacttct ctgggcatgt cttcactgtg cgcaagaagg aggagtacaa gatggccctg 3300

tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc 3360

tggagggtgg agtgcctcat tggggagcac ctgcatgctg gcatgagcac cctgttcctg 3420

gtctacagca acaagtgcca gacccccctg ggaatggcct ctggccacat cagggacttc 3480

cagatcactg cctctggcca gtatggccag tgggccccca agctggccag gctccactac 3540

tctggatcca tcaatgcctg gagcaccaag gagccattca gctggatcaa agtggacctg 3600

ctggccccca tgatcatcca tggcatcaag acccaggggg ccaggcagaa gttctccagc 3660

ctgtacatca gccagttcat catcatgtac agcctggatg gcaagaaatg gcagacctac 3720

agaggcaact ccactggaac actcatggtc ttctttggca atgtggacag ctctggcatc 3780

aagcacaaca tcttcaaccc cccaatcatc gccagataca tcaggctgca ccccacccac 3840

tacagcatcc gcagcaccct caggatggag ctgatgggct gtgacctgaa ctcctgcagc 3900

atgcccctgg gcatggagag caaggccatt tctgatgccc agatcactgc ctccagctac 3960

ttcaccaaca tgtttgccac ctggagccca agcaaggcca ggctgcacct ccagggaagg 4020

agcaatgcct ggaggcccca ggtcaacaac ccaaaggagt ggctgcaggt ggacttccag 4080

-continued

aagaccatga aggtcactgg ggtgaccacc caggggtca agagcctgct caccagcatg 4140

tatgtgaagg agttcctgat cagctccagc caggatggcc accagtggac cctcttcttc 4200

cagaatggca aggtcaaggt gttccagggc aaccaggaca gcttcacccc tgtggtgaac 4260

agcctggacc ccccctcct gaccagatac ctgaggattc acccccagag ctgggtccac 4320

cagattgccc tgaggatgga ggtcctggga tgtgaggccc aggacctgta ctga 4374

<210> SEQ ID NO 98
<211> LENGTH: 4377
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 98

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcatcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaaggc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg ggcagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccatggc ctctgaccca ctctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gtcctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

-continued

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

agctatgagg acatctctgc ctacctgctc agcaagaaca ataccaccta cgtgaaccgc 2280

tccctgagcc agaatccacc tgtcctgaaa cgccaccaga gggagatcac caggaccacc 2340

ctccagtctg accaggagga gattgactat gatgacacca tttctgtgga gatgaagaaa 2400

gaggactttg acatctatga cgaggacgag aaccagagcc caaggagctt ccagaagaag 2460

accaggcact acttcattgc tgctgtggag cgcctgtggg actatggcat gagctccagc 2520

ccccatgtcc tcaggaacag ggcccagtct ggctctgtgc cacagttcaa gaaagtggtc 2580

ttccaagagt tcactgatgg cagcttcacc cagcccctgt acagagggga gctgaatgag 2640

cacctgggac tcctgggccc atacatcagg gctgaggtgg aggacaacat catggtgacc 2700

ttccgcaacc aggcctccag gccctacagc ttctacagct ccctcatcag ctatgaggag 2760

gaccagaggc aggggggctga gccacgcaag aactttgtga aacccaatga aaccaagacc 2820

tacttctgga aagtccagca ccacatggcc cccaccaagg atgagtttga ctgcaaggcc 2880

tgggcctact tctctgatgt ggacctggag aaggatgtgc actctggcct gattggccca 2940

ctcctggtct gccacaccaa caccctgaac cctgcccatg gaaggcaagt gactgtgcag 3000

gagtttgccc tcttcttcac catctttgat gaaaccaaga gctggtactt cactgagaac 3060

atggagcgca actgcagggc cccatgcaac attcagatgg aggaccccac cttcaaagag 3120

aactaccgct tccatgccat caatggctac atcatggaca ccctgcctgg gcttgtcatg 3180

gcccaggacc agaggatcag gtggtacctg ctttctatgg gctccaatga gaacattcac 3240

tccatccact tctctgggca tgtcttcact gtgcgcaaga aggaggagta caagatggcc 3300

ctgtacaacc tctaccctgg ggtctttgag actgtggaga tgctgccctc caaagctggc 3360

atctggaggg tggagtgcct cattggggag cacctgcatg ctggcatgag caccctgttc 3420

ctggtctaca gcaacaagtg ccagaccccc ctgggaatgg cctctggcca catcagggac 3480

ttccagatca ctgcctctgg ccagtatggc cagtgggccc ccaagctggc caggctccac 3540

tactctggat ccatcaatgc ctggagcacc aaggagccat tcagctggat caaagtggac 3600

ctgctggccc ccatgatcat ccatggcatc aagacccagg gggccaggca gaagttctcc 3660

agcctgtaca tcagccagtt catcatcatg tacagcctgg atggcaagaa atggcagacc 3720

tacagaggca actccactgg aacactcatg gtcttctttg gcaatgtgga cagctctggc 3780

atcaagcaca acatcttcaa ccccccaatc atcgccagat acatcaggct gcaccccacc 3840

cactacagca tccgcagcac cctcaggatg gagctgatgg gctgtgacct gaactcctgc 3900

-continued

agcatgcccc tgggcatgga gagcaaggcc atttctgatg cccagatcac tgcctccagc 3960

tacttcacca acatgtttgc cacctggagc ccaagcaagg ccaggctgca cctccaggga 4020

aggagcaatg cctggaggcc ccaggtcaac aacccaaagg agtggctgca ggtggacttc 4080

cagaagacca tgaaggtcac tggggtgacc acccaggggg tcaagagcct gctcaccagc 4140

atgtatgtga aggagttcct gatcagctcc agccaggatg gccaccagtg gaccctcttc 4200

ttccagaatg gcaaggtcaa ggtgttccag ggcaaccagg acagcttcac ccctgtggtg 4260

aacagcctgg acccccccct cctgaccaga tacctgagga ttcaccccca gagctgggtc 4320

caccagattg ccctgaggat ggaggtcctg ggatgtgagg cccaggacct gtactga 4377

<210> SEQ ID NO 99
<211> LENGTH: 4377
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 99

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg 120

ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac 180

acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc 240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac 300

gacaccgtgg tgatcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg 360

ggcgtgagct actggaaggc ctctgagggc gccgagtatg acgaccagac cagccagagg 420

gagaaggagg acgacaaggt gttccccggc ggcagccaca cctacgtgtg gcaggtgctg 480

aaggagaacg gccccatggc cagcgacccc ctgtgcctga cctacagcta cctgagccac 540

gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag 600

ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg 660

ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat 720

gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc 780

ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc 840

accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac 900

aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg 960

gacctgggcc agttcctgct gtcctgccac atcagcagcc accagcacga cggcatggag 1020

gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag 1080

gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat 1140

gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc 1200

tgggtgcact acatcgccgc cgaggaggag gactgggact acgccccct ggtgctggcc 1260

cccgacgaca ggagctacaa gagccagtac ctgaacaacg gcccccagag gatcggcagg 1320

aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc 1380

atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg 1440

ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctaccccca cggcatcacc 1500

-continued

gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc 1620

accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg 1680

gacctggcct ctggcctgat cggcccctg ctgatctgct acaaggagag cgtggaccag 1740

aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag 1800

aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg 1860

cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg 1920

ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc 2100

atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc 2160

atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg acatcagcgc ctacctgctg agcaagaaca acaccaccta cgtgaaccgc 2280

tccctgagcc agaaccccc cgtgctgaag aggcaccaga gggagatcac caggaccacc 2340

ctgcagagcg accaggagga gatcgactat gatgacacca tcagcgtgga gatgaagaag 2400

gaggacttcg acatctacga cgaggacgag aaccagagcc ccaggagctt ccagaagaag 2460

accaggcact acttcatcgc cgccgtggag aggctgtggg actatggcat gagcagcagc 2520

ccccacgtgc tgaggaacag ggcccagagc ggcagcgtgc cccagttcaa gaaggtggtg 2580

ttccaggagt tcaccgacgg cagcttcacc cagcccctgt acagaggcga gctgaacgag 2640

cacctgggcc tgctgggccc ctacatcagg gccgaggtgg aggacaacat catggtgacc 2700

ttcaggaacc aggccagcag gccctacagc ttctacagca gcctgatcag ctacgaggag 2760

gaccagaggc agggcgccga gcccaggaag aacttcgtga agcccaacga gaccaagacc 2820

tacttctgga aggtgcagca ccacatggcc cccaccaagg acgagttcga ctgcaaggcc 2880

tgggcctact tctctgatgt ggacctggag aaggacgtgc acagcggcct gatcggcccc 2940

ctgctggtgt gccacaccaa caccctgaac cccgcccacg gcaggcaggt gaccgtgcag 3000

gagttcgccc tgttcttcac catcttcgac gagaccaaga gctggtactt caccgagaac 3060

atggagagga actgcagggc cccctgcaac atccagatgg aggaccccac cttcaaggag 3120

aactacaggt tccacgccat caacggctac atcatggaca ccctgcccgg cctggtgatg 3180

gcccaggacc agaggatcag gtggtatctg ctgagcatgg gcagcaacga gaacatccac 3240

agcatccact tcagcggcca cgtgttcacc gtgaggaaga aggaggagta caagatggcc 3300

ctgtacaacc tgtaccccgg cgtgttcgag accgtggaga tgctgcccag caaggccggc 3360

atctggaggg tggagtgcct gatcggcgag cacctgcacg ccggcatgag caccctgttc 3420

ctggtgtaca gcaacaagtg ccagaccccc ctgggcatgg ccagcggcca catcagggac 3480

ttccagatca ccgcctctgg ccagtacggc cagtgggccc ccaagctggc caggctgcac 3540

tacagcggca gcatcaacgc ctggagcacc aaggagccct tcagctggat caaggtggac 3600

ctgctggccc ccatgatcat ccacggcatc aagacccagg gcgccaggca gaagttcagc 3660

agcctgtaca tcagccagtt catcatcatg tacagcctgg acggcaagaa gtggcagacc 3720

tacaggggca acagcaccgg caccctgatg gtgttcttcg gcaacgtgga cagcagcggc 3780

-continued

atcaagcaca acatcttcaa ccccccccatc atcgccaggt acatcaggct gcaccccacc 3840

cactacagca tcaggagcac cctgcggatg gaactgatgg gctgcgacct gaacagctgc 3900

agcatgcccc tgggcatgga gagcaaggcc atctctgacg cccagatcac cgccagcagc 3960

tacttcacca acatgttcgc cacctggagc cccagcaagg ccaggctgca cctgcagggc 4020

aggagcaacg cctggaggcc ccaggtgaac aaccccaagg agtggctgca ggtggacttc 4080

cagaagacca tgaaggtgac cggcgtgacc acccagggcg tgaagagcct gctgaccagc 4140

atgtacgtga aggagttcct gatcagcagc agccaggacg gccaccagtg gaccctgttc 4200

ttccagaacg gcaaagtgaa ggtgttccag ggcaaccagg acagcttcac ccccgtggtg 4260

aacagcctgg acccccccct gctgaccagg tatctgagga tccaccccca gagctgggtg 4320

caccagatcg ccctgagaat ggaagtgctg ggatgcgagg cccaggacct gtactga 4377

<210> SEQ ID NO 100
<211> LENGTH: 4377
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 100

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg 120

ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac 180

acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc 240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac 300

gacaccgtgg tgatcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg 360

ggcgtgagct actggaaggc ctctgagggc gccgagtatg acgaccagac cagccagagg 420

gagaaggagg acgacaaggt gttccccggc ggcagccaca cctacgtgtg gcaggtgctg 480

aaggagaacg gccccatggc cagcgacccc ctgtgcctga cctacagcta cctgagccac 540

gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag 600

ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg 660

ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat 720

gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc 780

ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc 840

accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac 900

aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg 960

gacctgggcc agttcctgct gttctgccac atcagcagcc accagcacga cggcatggag 1020

gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag 1080

gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat 1140

gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc 1200

tgggtgcact acatcgccgc cgaggaggag gactgggact acgccccccct ggtgctggcc 1260

cccgacgaca ggagctacaa gagccagtac ctgaacaacg gcccccagag gatcggcagg 1320

-continued

aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc 1380

atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg 1440

ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctaccccca cggcatcacc 1500

gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc 1620

accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg 1680

gacctggcct ctggcctgat cggccccctg ctgatctgct acaaggagag cgtggaccag 1740

aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag 1800

aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg 1860

cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg 1920

ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc 2100

atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc 2160

atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg acatcagcgc ctacctgctg agcaagaaca acaccaccta cgtgaaccgc 2280

tccctgagcc agaacccccc cgtgctgaag aggcaccaga gggagatcac caggaccacc 2340

ctgcagagcg accaggagga gatcgactat gatgacacca tcagcgtgga gatgaagaag 2400

gaggacttcg acatctacga cgaggacgag aaccagagcc ccaggagctt ccagaagaag 2460

accaggcact acttcatcgc cgccgtggag aggctgtggg actatggcat gagcagcagc 2520

ccccacgtgc tgaggaacag ggcccagagc ggcagcgtgc cccagttcaa gaaggtggtg 2580

ttccaggagt tcaccgacgg cagcttcacc cagcccctgt acagaggcga gctgaacgag 2640

cacctgggcc tgctgggccc ctacatcagg gccgaggtgg aggacaacat catggtgacc 2700

ttcaggaacc aggccagcag gccctacagc ttctacagca gcctgatcag ctacgaggag 2760

gaccagaggc agggcgccga gcccaggaag aacttcgtga agcccaacga gaccaagacc 2820

tacttctgga aggtgcagca ccacatggcc cccaccaagg acgagttcga ctgcaaggcc 2880

tgggcctact tctctgatgt ggacctggag aaggacgtgc acagcggcct gatcggcccc 2940

ctgctggtgt gccacaccaa caccctgaac cccgcccacg gcaggcaggt gaccgtgcag 3000

gagttcgccc tgttcttcac catcttcgac gagaccaaga gctggtactt caccgagaac 3060

atggagagga actgcagggc cccctgcaac atccagatgg aggaccccac cttcaaggag 3120

aactacaggt tccacgccat caacggctac atcatggaca ccctgcccgg cctggtgatg 3180

gcccaggacc agaggatcag gtggtatctg ctgagcatgg gcagcaacga gaacatccac 3240

agcatccact tcagcggcca cgtgttcacc gtgaggaaga aggaggagta caagatggcc 3300

ctgtacaacc tgtaccccgg cgtgttcgag accgtggaga tgctgcccag caaggccggc 3360

atctggaggg tggagtgcct gatcggcgag cacctgcacg ccggcatgag caccctgttc 3420

ctggtgtaca gcaacaagtg ccagaccccc ctgggcatgg ccagcggcca catcagggac 3480

ttccagatca ccgcctctgg ccagtacggc cagtgggccc ccaagctggc caggctgcac 3540

tacagcggca gcatcaacgc ctggagcacc aaggagccct tcagctggat caaggtggac 3600

-continued

ctgctggccc ccatgatcat ccacggcatc aagacccagg gcgccaggca gaagttcagc 3660

agcctgtaca tcagccagtt catcatcatg tacagcctgg acggcaagaa gtggcagacc 3720

tacaggggca acagcaccgg caccctgatg gtgttcttcg gcaacgtgga cagcagcggc 3780

atcaagcaca acatcttcaa ccccccccatc atcgccaggt acatcaggct gcaccccacc 3840

cactacagca tcaggagcac cctgcggatg gaactgatgg gctgcgacct gaacagctgc 3900

agcatgcccc tgggcatgga gagcaaggcc atctctgacg cccagatcac cgccagcagc 3960

tacttcacca acatgttcgc cacctggagc cccagcaagg ccaggctgca cctgcagggc 4020

aggagcaacg cctggaggcc ccaggtgaac aaccccaagg agtggctgca ggtggacttc 4080

cagaagacca tgaaggtgac cggcgtgacc acccagggcg tgaagagcct gctgaccagc 4140

atgtacgtga aggagttcct gatcagcagc agccaggacg gccaccagtg gaccctgttc 4200

ttccagaacg gcaaagtgaa ggtgttccag ggcaaccagg acagcttcac ccccgtggtg 4260

aacagcctgg acccccccct gctgaccagg tatctgagga tccaccccca gagctgggtg 4320

caccagatcg ccctgagaat ggaagtgctg ggatgcgagg cccaggacct gtactga 4377

<210> SEQ ID NO 101
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 101

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg 120

ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac 180

acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc 240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac 300

gacaccgtgg tggtcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg 360

ggcgtgagct actggaagtc ctctgagggc gccgagtatg acgaccagac cagccagagg 420

gagaaggagg acgacaaggt gttccccggc aagagccaca cctacgtgtg gcaggtgctg 480

aaggagaacg gccccactgc cagcgacccc ccctgcctga cctacagcta cctgagccac 540

gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag 600

ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg 660

ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat 720

gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc 780

ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc 840

accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac 900

aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg 960

gacctgggcc agttcctgct gttctgccac atcagcagcc accagcacga cggcatggag 1020

gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag 1080

gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat 1140

gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc 1200

-continued

tgggtgcact acatcgccgc cgaggaggag gactgggact acgccccccct ggtgctggcc 1260

cccgacgaca ggagctacaa gagccagtac ctgaacaacg gcccccagag gatcggcagg 1320

aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc 1380

atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg 1440

ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctaccccca cggcatcacc 1500

gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc 1620

accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg 1680

gacctggcct ctggcctgat cggcccctg ctgatctgct acaaggagag cgtggaccag 1740

aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag 1800

aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg 1860

cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg 1920

ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc 2100

atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc 2160

atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg acatcagcgc ctacctgctg agcaagaaca acgccatcga gcccaggagc 2280

ttcagccaga accccccgt gctgaagagg caccagaggg agatcaccag gaccaccctg 2340

cagagcgacc aggaggagat cgactatgat gacaccatca gcgtggagat gaagaaggag 2400

gacttcgaca tctacgacga ggacgagaac cagagcccca ggagcttcca gaagaagacc 2460

aggcactact tcatcgccgc cgtggagagg ctgtgggact atggcatgag cagcagcccc 2520

cacgtgctga ggaacagggc ccagagcggc agcgtgcccc agttcaagaa ggtggtgttc 2580

caggagttca ccgacggcag cttcacccag cccctgtaca gaggcgagct gaacgagcac 2640

ctgggcctgc tgggccccta catcagggcc gaggtggagg acaacatcat ggtgaccttc 2700

aggaaccagg ccagcaggcc ctacagcttc tacagcagcc tgatcagcta cgaggaggac 2760

cagaggcagg gcgccgagcc caggaagaac ttcgtgaagc ccaacgagac caagacctac 2820

ttctggaagg tgcagcacca catggccccc accaaggacg agttcgactg caaggcctgg 2880

gcctacttct ctgatgtgga cctggagaag gacgtgcaca gcggcctgat cggcccctg 2940

ctggtgtgcc acaccaacac cctgaacccc gcccacggca ggcaggtgac cgtgcaggag 3000

ttcgccctgt tcttcaccat cttcgacgag accaagagct ggtacttcac cgagaacatg 3060

gagaggaact gcagggcccc ctgcaacatc cagatggagg accccacctt caaggagaac 3120

tacaggttcc acgccatcaa cggctacatc atggacaccc tgcccggcct ggtgatggcc 3180

caggaccaga ggatcaggtg gtatctgctg agcatgggca gcaacgagaa catccacagc 3240

atccacttca gcggccacgt gttcaccgtg aggaagaagg aggagtacaa gatggccctg 3300

tacaacctgt accccggcgt gttcgagacc gtggagatgc tgcccagcaa ggccggcatc 3360

tggagggtgg agtgcctgat cggcgagcac ctgcacgccg gcatgagcac cctgttcctg 3420

gtgtacagca acaagtgcca gacccccctg ggcatggcca gcggccacat cagggacttc 3480

-continued

cagatcaccg cctctggcca gtacggccag tgggccccca agctggccag gctgcactac 3540

agcggcagca tcaacgcctg gagcaccaag gagcccttca gctggatcaa ggtggacctg 3600

ctggccccca tgatcatcca cggcatcaag acccagggcg ccaggcagaa gttcagcagc 3660

ctgtacatca gccagttcat catcatgtac agcctggacg gcaagaagtg gcagacctac 3720

aggggcaaca gcaccggcac cctgatggtg ttcttcggca acgtggacag cagcggcatc 3780

aagcacaaca tcttcaaccc ccccatcatc gccaggtaca tcaggctgca ccccacccac 3840

tacagcatca ggagcaccct gcggatggaa ctgatgggct gcgacctgaa cagctgcagc 3900

atgcccctgg gcatggagag caaggccatc tctgacgccc agatcaccgc cagcagctac 3960

ttcaccaaca tgttcgccac ctggagcccc agcaaggcca ggctgcacct gcagggcagg 4020

agcaacgcct ggaggcccca ggtgaacaac cccaaggagt ggctgcaggt ggacttccag 4080

aagaccatga aggtgaccgg cgtgaccacc cagggcgtga agagcctgct gaccagcatg 4140

tacgtgaagg agttcctgat cagcagcagc caggacggcc accagtggac cctgttcttc 4200

cagaacggca aagtgaaggt gttccagggc aaccaggaca gcttcacccc cgtggtgaac 4260

agcctggacc ccccctgct gaccaggtat ctgaggatcc acccccagag ctgggtgcac 4320

cagatcgccc tgagaatgga agtgctggga tgcgaggccc aggacctgta ctga 4374

<210> SEQ ID NO 102
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 102

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg 120

ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac 180

acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc 240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac 300

gacaccgtgg tgatcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg 360

ggcgtgagct actggaaggc ctctgagggc gccgagtatg acgaccagac cagccagagg 420

gagaaggagg acgacaaggt gttccccggc ggcagccaca cctacgtgtg gcaggtgctg 480

aaggagaacg gccccatggc cagcgacccc ctgtgcctga cctacagcta cctgagccac 540

gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag 600

ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg 660

ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat 720

gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc 780

ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc 840

accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac 900

aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg 960

gacctgggcc agttcctgct gtcctgccac atcagcagcc accagcacga cggcatggag 1020

-continued

gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag 1080

gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat 1140

gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc 1200

tgggtgcact acatcgccgc cgaggaggag gactgggact acgccccccct ggtgctggcc 1260

cccgacgaca ggagctacaa gagccagtac ctgaacaacg gcccccagag gatcggcagg 1320

aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc 1380

atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg 1440

ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctaccccca cggcatcacc 1500

gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc 1620

accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg 1680

gacctggcct ctggcctgat cggcccctg ctgatctgct acaaggagag cgtggaccag 1740

aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag 1800

aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg 1860

cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg 1920

ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc 2100

atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc 2160

atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg acatcagcgc ctacctgctg agcaagaaca acgccatcga gcccaggagc 2280

ttcagccaga accccccccgt gctgaagagg caccagaggg agatcaccag gaccaccctg 2340

cagagcgacc aggaggagat cgactatgat gacaccatca gcgtggagat gaagaaggag 2400

gacttcgaca tctacgacga ggacgagaac cagagcccca ggagcttcca gaagaagacc 2460

aggcactact tcatcgccgc cgtggagagg ctgtgggact atggcatgag cagcagcccc 2520

cacgtgctga ggaacagggc ccagagcggc agcgtgcccc agttcaagaa ggtggtgttc 2580

caggagttca ccgacggcag cttcacccag cccctgtaca gaggcgagct gaacgagcac 2640

ctgggcctgc tgggccccta catcagggcc gaggtggagg acaacatcat ggtgaccttc 2700

aggaaccagg ccagcaggcc ctacagcttc tacagcagcc tgatcagcta cgaggaggac 2760

cagaggcagg gcgccgagcc caggaagaac ttcgtgaagc ccaacgagac caagacctac 2820

ttctggaagg tgcagcacca catggccccc accaaggacg agttcgactg caaggcctgg 2880

gcctacttct ctgatgtgga cctggagaag gacgtgcaca gcggcctgat cggcccccctg 2940

ctggtgtgcc acaccaacac cctgaacccc gcccacggca ggcaggtgac cgtgcaggag 3000

ttcgccctgt tcttcaccat cttcgacgag accaagagct ggtacttcac cgagaacatg 3060

gagaggaact gcagggcccc ctgcaacatc cagatggagg accccacctt caaggagaac 3120

tacaggttcc acgccatcaa cggctacatc atggacaccc tgcccggcct ggtgatggcc 3180

caggaccaga ggatcaggtg gtatctgctg agcatgggca gcaacgagaa catccacagc 3240

atccacttca gcggccacgt gttcaccgtg aggaagaagg aggagtacaa gatggccctg 3300

-continued

tacaacctgt accccggcgt gttcgagacc gtggagatgc tgcccagcaa ggccggcatc 3360

tggagggtgg agtgcctgat cggcgagcac ctgcacgccg gcatgagcac cctgttcctg 3420

gtgtacagca acaagtgcca gacccccctg ggcatggcca gcggccacat cagggacttc 3480

cagatcaccg cctctggcca gtacggccag tgggccccca agctggccag gctgcactac 3540

agcggcagca tcaacgcctg gagcaccaag gagcccttca gctggatcaa ggtggacctg 3600

ctggccccca tgatcatcca cggcatcaag acccagggcg ccaggcagaa gttcagcagc 3660

ctgtacatca gccagttcat catcatgtac agcctggacg gcaagaagtg gcagacctac 3720

aggggcaaca gcaccggcac cctgatggtg ttcttcggca acgtggacag cagcggcatc 3780

aagcacaaca tcttcaaccc ccccatcatc gccaggtaca tcaggctgca ccccacccac 3840

tacagcatca ggagcaccct gcggatggaa ctgatgggct gcgacctgaa cagctgcagc 3900

atgcccctgg gcatggagag caaggccatc tctgacgccc agatcaccgc cagcagctac 3960

ttcaccaaca tgttcgccac ctggagcccc agcaaggcca ggctgcacct gcagggcagg 4020

agcaacgcct ggaggcccca ggtgaacaac cccaaggagt ggctgcaggt ggacttccag 4080

aagaccatga aggtgaccgg cgtgaccacc cagggcgtga agagcctgct gaccagcatg 4140

tacgtgaagg agttcctgat cagcagcagc caggacggcc accagtggac cctgttcttc 4200

cagaacggca aagtgaaggt gttccagggc aaccaggaca gcttcacccc cgtggtgaac 4260

agcctggacc ccccccctgct gaccaggtat ctgaggatcc acccccagag ctgggtgcac 4320

cagatcgccc tgagaatgga agtgctggga tgcgaggccc aggacctgta ctga 4374

<210> SEQ ID NO 103
<211> LENGTH: 4377
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 103

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg cgccgtggag ctgagctggg actacatgca gtctgacctg 120

ggcgagctgc ctgtggacgc caggttcccc cccagagtgc ccaagagctt ccccttcaac 180

acctcagtgg tgtacaagaa gaccctgttc gtggagttca ccgaccacct gttcaacatc 240

gccaagccca ggcccccctg gatgggcctg ctgggcccca ccatccaggc cgaggtgtac 300

gacaccgtgg tggtcaccct gaagaacatg gccagccacc ccgtgagcct gcacgccgtg 360

ggcgtgagct actggaagtc ctctgagggc gccgagtatg acgaccagac cagccagagg 420

gagaaggagg acgacaaggt gttccccggc aagagccaca cctacgtgtg gcaggtgctg 480

aaggagaacg gccccactgc cagcgacccc ccctgcctga cctacagcta cctgagccac 540

gtggacctgg tgaaggacct gaactctggc ctgatcggcg ccctgctggt gtgcagggag 600

ggcagcctgg ccaaggagaa gacccagacc ctgcacaagt tcatcctgct gttcgccgtg 660

ttcgatgagg gcaagagctg gcacagcgag accaagaaca gcctgatgca ggacagggat 720

gccgcctctg ccagggcctg gcccaagatg cacaccgtga acggctacgt gaacaggagc 780

ctgcccggcc tgatcggctg ccacaggaag tctgtgtact ggcacgtgat cggcatgggc 840

accacccccg aggtgcacag catcttcctg gagggccaca ccttcctggt gaggaaccac 900

-continued

aggcaggcca gcctggagat cagccccatc accttcctga ccgcccagac cctgctgatg 960

gacctgggcc agttcctgct gttctgccac atcagcagcc accagcacga cggcatggag 1020

gcctacgtga aggtggacag ctgccccgag gagccccagc tgaggatgaa gaacaacgag 1080

gaggccgagg actatgatga tgacctgacc gactctgaga tggacgtggt gaggtttgat 1140

gatgacaaca gccccagctt catccagatc aggtctgtgg ccaagaagca ccccaagacc 1200

tgggtgcact acatcgccgc cgaggaggag gactgggact acgccccccct ggtgctggcc 1260

cccgacgaca ggagctacaa gagccagtac ctgaacaacg gcccccagag gatcggcagg 1320

aagtacaaga aggtcagatt catggcctac accgacgaga ccttcaagac cagggaggcc 1380

atccagcacg agtctggcat cctgggcccc ctgctgtacg gcgaggtggg cgacaccctg 1440

ctgatcatct tcaagaacca ggccagcagg ccctacaaca tctaccccca cggcatcacc 1500

gatgtgaggc ccctgtacag caggaggctg cccaagggcg tgaagcacct gaaggacttc 1560

cccatcctgc ccggcgagat cttcaagtac aagtggaccg tgaccgtgga ggatggcccc 1620

accaagtctg accccaggtg cctgaccagg tactacagca gcttcgtgaa catggagagg 1680

gacctggcct ctggcctgat cggcccccctg ctgatctgct acaaggagag cgtggaccag 1740

aggggcaacc agatcatgtc tgacaagagg aacgtgatcc tgttctctgt gttcgatgag 1800

aacaggagct ggtatctgac cgagaacatc cagaggttcc tgcccaaccc cgccggcgtg 1860

cagctggagg accccgagtt ccaggccagc aacatcatgc acagcatcaa cggctacgtg 1920

ttcgacagcc tgcagctgtc tgtgtgcctg cacgaggtgg cctactggta catcctgagc 1980

atcggcgccc agaccgactt cctgtctgtg ttcttctctg gctacacctt caagcacaag 2040

atggtgtacg aggacaccct gaccctgttc cccttcagcg gcgagaccgt gttcatgagc 2100

atggagaacc ccggcctgtg gatcctgggc tgccacaaca gcgacttcag gaacaggggc 2160

atgaccgccc tgctgaaagt cagcagctgc gacaagaaca ccggcgacta ctacgaggac 2220

agctacgagg acatcagcgc ctacctgctg agcaagaaca acaccaccta cgtgaaccgc 2280

tccctgagcc agaaccccccc cgtgctgaag aggcaccaga gggagatcac caggaccacc 2340

ctgcagagcg accaggagga gatcgactat gatgacacca tcagcgtgga gatgaagaag 2400

gaggacttcg acatctacga cgaggacgag aaccagagcc ccaggagctt ccagaagaag 2460

accaggcact acttcatcgc cgccgtggag aggctgtggg actatggcat gagcagcagc 2520

ccccacgtgc tgaggaacag ggcccagagc ggcagcgtgc cccagttcaa gaaggtggtg 2580

ttccaggagt tcaccgacgg cagcttcacc cagcccctgt acagaggcga gctgaacgag 2640

cacctgggcc tgctgggccc ctacatcagg gccgaggtgg aggacaacat catggtgacc 2700

ttcaggaacc aggccagcag gccctacagc ttctacagca gcctgatcag ctacgaggag 2760

gaccagaggc agggcgccga gcccaggaag aacttcgtga agcccaacga gaccaagacc 2820

tacttctgga aggtgcagca ccacatggcc cccaccaagg acgagttcga ctgcaaggcc 2880

tgggcctact tctctgatgt ggacctggag aaggacgtgc acagcggcct gatcggcccc 2940

ctgctggtgt gccacaccaa caccctgaac cccgcccacg gcaggcaggt gaccgtgcag 3000

gagttcgccc tgttcttcac catcttcgac gagaccaaga gctggtactt caccgagaac 3060

atggagagga actgcagggc cccctgcaac atccagatgg aggaccccac cttcaaggag 3120

aactacaggt tccacgccat caacggctac atcatggaca ccctgcccgg cctggtgatg 3180

-continued

gcccaggacc agaggatcag gtggtatctg ctgagcatgg gcagcaacga gaacatccac 3240

agcatccact tcagcggcca cgtgttcacc gtgaggaaga aggaggagta caagatggcc 3300

ctgtacaacc tgtaccccgg cgtgttcgag accgtggaga tgctgcccag caaggccggc 3360

atctggaggg tggagtgcct gatcggcgag cacctgcacg ccggcatgag caccctgttc 3420

ctggtgtaca gcaacaagtg ccagaccccc ctgggcatgg ccagcggcca catcagggac 3480

ttccagatca ccgcctctgg ccagtacggc cagtgggccc ccaagctggc caggctgcac 3540

tacagcggca gcatcaacgc ctggagcacc aaggagccct tcagctggat caaggtggac 3600

ctgctggccc ccatgatcat ccacggcatc aagacccagg gcgccaggca gaagttcagc 3660

agcctgtaca tcagccagtt catcatcatg tacagcctgg acggcaagaa gtggcagacc 3720

tacaggggca acagcaccgg caccctgatg gtgttcttcg gcaacgtgga cagcagcggc 3780

atcaagcaca acatcttcaa cccccccatc atcgccaggt acatcaggct gcaccccacc 3840

cactacagca tcaggagcac cctgcggatg gaactgatgg gctgcgacct gaacagctgc 3900

agcatgcccc tgggcatgga gagcaaggcc atctctgacg cccagatcac cgccagcagc 3960

tacttcacca acatgttcgc cacctggagc cccagcaagg ccaggctgca cctgcagggc 4020

aggagcaacg cctggaggcc ccaggtgaac aaccccaagg agtggctgca ggtggacttc 4080

cagaagacca tgaaggtgac cggcgtgacc acccagggcg tgaagagcct gctgaccagc 4140

atgtacgtga aggagttcct gatcagcagc agccaggacg gccaccagtg gaccctgttc 4200

ttccagaacg gcaaagtgaa ggtgttccag ggcaaccagg acagcttcac ccccgtggtg 4260

aacagcctgg acccccccct gctgaccagg tatctgagga tccacccca gagctgggtg 4320

caccagatcg ccctgagaat ggaagtgctg ggatgcgagg cccaggacct gtactga 4377

<210> SEQ ID NO 104
<211> LENGTH: 1458
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 104

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Val Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ser Ser
115 120 125

-continued

```
Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
    130                 135                 140

Asp Lys Val Phe Pro Gly Lys Ser His Thr Tyr Val Trp Gln Val Leu
145                 150                 155                 160

Lys Glu Asn Gly Pro Thr Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser
                165                 170                 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
            180                 185                 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
        195                 200                 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
    210                 215                 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225                 230                 235                 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
                245                 250                 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
            260                 265                 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
        275                 280                 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
    290                 295                 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305                 310                 315                 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
                325                 330                 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
            340                 345                 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
                405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
                485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
```

-continued

```
    530                 535                 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
                565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
                645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
            660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
        675                 680                 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
    690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705                 710                 715                 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
                725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
            740                 745                 750

Asn Asn Thr Thr Tyr Val Asn Arg Ser Leu Ser Gln Asn Pro Pro Val
        755                 760                 765

Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp
    770                 775                 780

Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys
785                 790                 795                 800

Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser
                805                 810                 815

Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu
            820                 825                 830

Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala
        835                 840                 845

Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe
    850                 855                 860

Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu
865                 870                 875                 880

His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn
                885                 890                 895

Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr
            900                 905                 910

Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro
        915                 920                 925

Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys
    930                 935                 940
```

-continued

```
Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala
945                 950                 955                 960

Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly
                965                 970                 975

Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala
            980                 985                 990

His Gly Arg Gln Val Thr Val Gln  Glu Phe Ala Leu Phe  Phe Thr Ile
        995                 1000                1005

Phe Asp  Glu Thr Lys Ser Trp  Tyr Phe Thr Glu Asn  Met Glu Arg
    1010                1015                1020

Asn Cys  Arg Ala Pro Cys Asn  Ile Gln Met Glu Asp  Pro Thr Phe
    1025                1030                1035

Lys Glu  Asn Tyr Arg Phe His  Ala Ile Asn Gly Tyr  Ile Met Asp
    1040                1045                1050

Thr Leu  Pro Gly Leu Val Met  Ala Gln Asp Gln Arg  Ile Arg Trp
    1055                1060                1065

Tyr Leu  Leu Ser Met Gly Ser  Asn Glu Asn Ile His  Ser Ile His
    1070                1075                1080

Phe Ser  Gly His Val Phe Thr  Val Arg Lys Lys Glu  Glu Tyr Lys
    1085                1090                1095

Met Ala  Leu Tyr Asn Leu Tyr  Pro Gly Val Phe Glu  Thr Val Glu
    1100                1105                1110

Met Leu  Pro Ser Lys Ala Gly  Ile Trp Arg Val Glu  Cys Leu Ile
    1115                1120                1125

Gly Glu  His Leu His Ala Gly  Met Ser Thr Leu Phe  Leu Val Tyr
    1130                1135                1140

Ser Asn  Lys Cys Gln Thr Pro  Leu Gly Met Ala Ser  Gly His Ile
    1145                1150                1155

Arg Asp  Phe Gln Ile Thr Ala  Ser Gly Gln Tyr Gly  Gln Trp Ala
    1160                1165                1170

Pro Lys  Leu Ala Arg Leu His  Tyr Ser Gly Ser Ile  Asn Ala Trp
    1175                1180                1185

Ser Thr  Lys Glu Pro Phe Ser  Trp Ile Lys Val Asp  Leu Leu Ala
    1190                1195                1200

Pro Met  Ile Ile His Gly Ile  Lys Thr Gln Gly Ala  Arg Gln Lys
    1205                1210                1215

Phe Ser  Ser Leu Tyr Ile Ser  Gln Phe Ile Ile Met  Tyr Ser Leu
    1220                1225                1230

Asp Gly  Lys Lys Trp Gln Thr  Tyr Arg Gly Asn Ser  Thr Gly Thr
    1235                1240                1245

Leu Met  Val Phe Phe Gly Asn  Val Asp Ser Ser Gly  Ile Lys His
    1250                1255                1260

Asn Ile  Phe Asn Pro Pro Ile  Ile Ala Arg Tyr Ile  Arg Leu His
    1265                1270                1275

Pro Thr  His Tyr Ser Ile Arg  Ser Thr Leu Arg Met  Glu Leu Met
    1280                1285                1290

Gly Cys  Asp Leu Asn Ser Cys  Ser Met Pro Leu Gly  Met Glu Ser
    1295                1300                1305

Lys Ala  Ile Ser Asp Ala Gln  Ile Thr Ala Ser Ser  Tyr Phe Thr
    1310                1315                1320
```

-continued

```
Asn Met  Phe Ala Thr Trp Ser  Pro Ser Lys Ala Arg  Leu His Leu
    1325                 1330                 1335

Gln Gly  Arg Ser Asn Ala Trp  Arg Pro Gln Val Asn  Asn Pro Lys
    1340                 1345                 1350

Glu Trp  Leu Gln Val Asp Phe  Gln Lys Thr Met Lys  Val Thr Gly
    1355                 1360                 1365

Val Thr  Thr Gln Gly Val Lys  Ser Leu Leu Thr Ser  Met Tyr Val
    1370                 1375                 1380

Lys Glu  Phe Leu Ile Ser Ser  Ser Gln Asp Gly His  Gln Trp Thr
    1385                 1390                 1395

Leu Phe  Phe Gln Asn Gly Lys  Val Lys Val Phe Gln  Gly Asn Gln
    1400                 1405                 1410

Asp Ser  Phe Thr Pro Val Val  Asn Ser Leu Asp Pro  Pro Leu Leu
    1415                 1420                 1425

Thr Arg  Tyr Leu Arg Ile His  Pro Gln Ser Trp Val  His Gln Ile
    1430                 1435                 1440

Ala Leu  Arg Met Glu Val Leu  Gly Cys Glu Ala Gln  Asp Leu Tyr
    1445                 1450                 1455


<210> SEQ ID NO 105
<211> LENGTH: 1458
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 105

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1               5                  10                  15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
            20                  25                  30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
        35                  40                  45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
    50                  55                  60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65                  70                  75                  80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
                85                  90                  95

Ala Glu Val Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser
            100                 105                 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ala Ser
        115                 120                 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
    130                 135                 140

Asp Lys Val Phe Pro Gly Gly Ser His Thr Tyr Val Trp Gln Val Leu
145                 150                 155                 160

Lys Glu Asn Gly Pro Met Ala Ser Asp Pro Leu Cys Leu Thr Tyr Ser
                165                 170                 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
            180                 185                 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
        195                 200                 205
```

-continued

```
Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
    210                 215                 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225                 230                 235                 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
                245                 250                 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
            260                 265                 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
        275                 280                 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
    290                 295                 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305                 310                 315                 320

Asp Leu Gly Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His
                325                 330                 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
            340                 345                 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
                405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
                485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
    530                 535                 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
                565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605
```

-continued

```
Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
                645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
            660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
        675                 680                 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
    690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705                 710                 715                 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
                725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
            740                 745                 750

Asn Asn Thr Thr Tyr Val Asn Arg Ser Leu Ser Gln Asn Pro Pro Val
        755                 760                 765

Leu Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp
    770                 775                 780

Gln Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys
785                 790                 795                 800

Glu Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser
                805                 810                 815

Phe Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu
            820                 825                 830

Trp Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala
        835                 840                 845

Gln Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe
    850                 855                 860

Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu
865                 870                 875                 880

His Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn
                885                 890                 895

Ile Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr
            900                 905                 910

Ser Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro
        915                 920                 925

Arg Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys
    930                 935                 940

Val Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala
945                 950                 955                 960

Trp Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly
                965                 970                 975

Leu Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala
            980                 985                 990

His Gly Arg Gln Val Thr Val Gln  Glu Phe Ala Leu Phe  Phe Thr Ile
        995                 1000                1005

Phe Asp  Glu Thr Lys Ser Trp  Tyr Phe Thr Glu Asn  Met Glu Arg
```

-continued

```
    1010                1015                1020

Asn Cys  Arg Ala Pro Cys Asn  Ile Gln Met Glu Asp  Pro Thr Phe
    1025                1030                1035

Lys Glu  Asn Tyr Arg Phe His  Ala Ile Asn Gly Tyr  Ile Met Asp
    1040                1045                1050

Thr Leu  Pro Gly Leu Val Met  Ala Gln Asp Gln Arg  Ile Arg Trp
    1055                1060                1065

Tyr Leu  Leu Ser Met Gly Ser  Asn Glu Asn Ile His  Ser Ile His
    1070                1075                1080

Phe Ser  Gly His Val Phe Thr  Val Arg Lys Lys Glu  Glu Tyr Lys
    1085                1090                1095

Met Ala  Leu Tyr Asn Leu Tyr  Pro Gly Val Phe Glu  Thr Val Glu
    1100                1105                1110

Met Leu  Pro Ser Lys Ala Gly  Ile Trp Arg Val Glu  Cys Leu Ile
    1115                1120                1125

Gly Glu  His Leu His Ala Gly  Met Ser Thr Leu Phe  Leu Val Tyr
    1130                1135                1140

Ser Asn  Lys Cys Gln Thr Pro  Leu Gly Met Ala Ser  Gly His Ile
    1145                1150                1155

Arg Asp  Phe Gln Ile Thr Ala  Ser Gly Gln Tyr Gly  Gln Trp Ala
    1160                1165                1170

Pro Lys  Leu Ala Arg Leu His  Tyr Ser Gly Ser Ile  Asn Ala Trp
    1175                1180                1185

Ser Thr  Lys Glu Pro Phe Ser  Trp Ile Lys Val Asp  Leu Leu Ala
    1190                1195                1200

Pro Met  Ile Ile His Gly Ile  Lys Thr Gln Gly Ala  Arg Gln Lys
    1205                1210                1215

Phe Ser  Ser Leu Tyr Ile Ser  Gln Phe Ile Ile Met  Tyr Ser Leu
    1220                1225                1230

Asp Gly  Lys Lys Trp Gln Thr  Tyr Arg Gly Asn Ser  Thr Gly Thr
    1235                1240                1245

Leu Met  Val Phe Phe Gly Asn  Val Asp Ser Ser Gly  Ile Lys His
    1250                1255                1260

Asn Ile  Phe Asn Pro Pro Ile  Ile Ala Arg Tyr Ile  Arg Leu His
    1265                1270                1275

Pro Thr  His Tyr Ser Ile Arg  Ser Thr Leu Arg Met  Glu Leu Met
    1280                1285                1290

Gly Cys  Asp Leu Asn Ser Cys  Ser Met Pro Leu Gly  Met Glu Ser
    1295                1300                1305

Lys Ala  Ile Ser Asp Ala Gln  Ile Thr Ala Ser Ser  Tyr Phe Thr
    1310                1315                1320

Asn Met  Phe Ala Thr Trp Ser  Pro Ser Lys Ala Arg  Leu His Leu
    1325                1330                1335

Gln Gly  Arg Ser Asn Ala Trp  Arg Pro Gln Val Asn  Asn Pro Lys
    1340                1345                1350

Glu Trp  Leu Gln Val Asp Phe  Gln Lys Thr Met Lys  Val Thr Gly
    1355                1360                1365

Val Thr  Thr Gln Gly Val Lys  Ser Leu Leu Thr Ser  Met Tyr Val
    1370                1375                1380

Lys Glu  Phe Leu Ile Ser Ser  Ser Gln Asp Gly His  Gln Trp Thr
    1385                1390                1395
```

-continued

```
Leu Phe  Phe Gln Asn Gly Lys  Val Lys Val Phe Gln  Gly Asn Gln
    1400                 1405                 1410

Asp Ser  Phe Thr Pro Val Val  Asn Ser Leu Asp Pro  Pro Leu Leu
    1415                 1420                 1425

Thr Arg  Tyr Leu Arg Ile His  Pro Gln Ser Trp Val  His Gln Ile
    1430                 1435                 1440

Ala Leu  Arg Met Glu Val Leu  Gly Cys Glu Ala Gln  Asp Leu Tyr
    1445                 1450                 1455


<210> SEQ ID NO 106
<211> LENGTH: 1457
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 106

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1               5                  10                  15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
            20                  25                  30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
        35                  40                  45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
    50                  55                  60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65                  70                  75                  80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
                85                  90                  95

Ala Glu Val Tyr Asp Thr Val Val Val Thr Leu Lys Asn Met Ala Ser
            100                 105                 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ser Ser
        115                 120                 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
    130                 135                 140

Asp Lys Val Phe Pro Gly Lys Ser His Thr Tyr Val Trp Gln Val Leu
145                 150                 155                 160

Lys Glu Asn Gly Pro Thr Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser
                165                 170                 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
            180                 185                 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
        195                 200                 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
    210                 215                 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225                 230                 235                 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
                245                 250                 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
            260                 265                 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
```

-continued

```
        275                 280                 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
    290                 295                 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305                 310                 315                 320

Asp Leu Gly Gln Phe Leu Leu Ser Cys His Ile Ser Ser His Gln His
                325                 330                 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
            340                 345                 350

Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
                405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
                485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
    530                 535                 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
                565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
                645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
            660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
        675                 680                 685
```

-continued

```
Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
    690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705                 710                 715                 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
                725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
            740                 745                 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
        755                 760                 765

Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln
    770                 775                 780

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
785                 790                 795                 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
                805                 810                 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
            820                 825                 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
        835                 840                 845

Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
    850                 855                 860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His
865                 870                 875                 880

Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile
                885                 890                 895

Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser
            900                 905                 910

Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
        915                 920                 925

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val
    930                 935                 940

Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
945                 950                 955                 960

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu
                965                 970                 975

Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His
            980                 985                 990

Gly Arg Gln Val Thr Val Gln Glu  Phe Ala Leu Phe Phe  Thr Ile Phe
        995                 1000                1005

Asp Glu  Thr Lys Ser Trp Tyr  Phe Thr Glu Asn Met  Glu Arg Asn
    1010                1015                1020

Cys Arg  Ala Pro Cys Asn Ile  Gln Met Glu Asp Pro  Thr Phe Lys
    1025                1030                1035

Glu Asn  Tyr Arg Phe His Ala  Ile Asn Gly Tyr Ile  Met Asp Thr
    1040                1045                1050

Leu Pro  Gly Leu Val Met Ala  Gln Asp Gln Arg Ile  Arg Trp Tyr
    1055                1060                1065

Leu Leu  Ser Met Gly Ser Asn  Glu Asn Ile His Ser  Ile His Phe
    1070                1075                1080
```

-continued

```
Ser Gly  His Val Phe Thr Val  Arg Lys Lys Glu Glu  Tyr Lys Met
    1085                1090                1095

Ala Leu  Tyr Asn Leu Tyr Pro  Gly Val Phe Glu Thr  Val Glu Met
    1100                1105                1110

Leu Pro  Ser Lys Ala Gly Ile  Trp Arg Val Glu Cys  Leu Ile Gly
    1115                1120                1125

Glu His  Leu His Ala Gly Met  Ser Thr Leu Phe Leu  Val Tyr Ser
    1130                1135                1140

Asn Lys  Cys Gln Thr Pro Leu  Gly Met Ala Ser Gly  His Ile Arg
    1145                1150                1155

Asp Phe  Gln Ile Thr Ala Ser  Gly Gln Tyr Gly Gln  Trp Ala Pro
    1160                1165                1170

Lys Leu  Ala Arg Leu His Tyr  Ser Gly Ser Ile Asn  Ala Trp Ser
    1175                1180                1185

Thr Lys  Glu Pro Phe Ser Trp  Ile Lys Val Asp Leu  Leu Ala Pro
    1190                1195                1200

Met Ile  Ile His Gly Ile Lys  Thr Gln Gly Ala Arg  Gln Lys Phe
    1205                1210                1215

Ser Ser  Leu Tyr Ile Ser Gln  Phe Ile Ile Met Tyr  Ser Leu Asp
    1220                1225                1230

Gly Lys  Lys Trp Gln Thr Tyr  Arg Gly Asn Ser Thr  Gly Thr Leu
    1235                1240                1245

Met Val  Phe Phe Gly Asn Val  Asp Ser Ser Gly Ile  Lys His Asn
    1250                1255                1260

Ile Phe  Asn Pro Pro Ile Ile  Ala Arg Tyr Ile Arg  Leu His Pro
    1265                1270                1275

Thr His  Tyr Ser Ile Arg Ser  Thr Leu Arg Met Glu  Leu Met Gly
    1280                1285                1290

Cys Asp  Leu Asn Ser Cys Ser  Met Pro Leu Gly Met  Glu Ser Lys
    1295                1300                1305

Ala Ile  Ser Asp Ala Gln Ile  Thr Ala Ser Ser Tyr  Phe Thr Asn
    1310                1315                1320

Met Phe  Ala Thr Trp Ser Pro  Ser Lys Ala Arg Leu  His Leu Gln
    1325                1330                1335

Gly Arg  Ser Asn Ala Trp Arg  Pro Gln Val Asn Asn  Pro Lys Glu
    1340                1345                1350

Trp Leu  Gln Val Asp Phe Gln  Lys Thr Met Lys Val  Thr Gly Val
    1355                1360                1365

Thr Thr  Gln Gly Val Lys Ser  Leu Leu Thr Ser Met  Tyr Val Lys
    1370                1375                1380

Glu Phe  Leu Ile Ser Ser Ser  Gln Asp Gly His Gln  Trp Thr Leu
    1385                1390                1395

Phe Phe  Gln Asn Gly Lys Val  Lys Val Phe Gln Gly  Asn Gln Asp
    1400                1405                1410

Ser Phe  Thr Pro Val Val Asn  Ser Leu Asp Pro Pro  Leu Leu Thr
    1415                1420                1425

Arg Tyr  Leu Arg Ile His Pro  Gln Ser Trp Val His  Gln Ile Ala
    1430                1435                1440

Leu Arg  Met Glu Val Leu Gly  Cys Glu Ala Gln Asp  Leu Tyr
    1445                1450                1455
```

-continued

<210> SEQ ID NO 107
<211> LENGTH: 1457
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 107

Met Gln Ile Glu Leu Ser Thr Cys Phe Phe Leu Cys Leu Leu Arg Phe
1 5 10 15

Cys Phe Ser Ala Thr Arg Arg Tyr Tyr Leu Gly Ala Val Glu Leu Ser
20 25 30

Trp Asp Tyr Met Gln Ser Asp Leu Gly Glu Leu Pro Val Asp Ala Arg
35 40 45

Phe Pro Pro Arg Val Pro Lys Ser Phe Pro Phe Asn Thr Ser Val Val
50 55 60

Tyr Lys Lys Thr Leu Phe Val Glu Phe Thr Asp His Leu Phe Asn Ile
65 70 75 80

Ala Lys Pro Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln
85 90 95

Ala Glu Val Tyr Asp Thr Val Val Val Thr Leu Lys Asn Met Ala Ser
100 105 110

His Pro Val Ser Leu His Ala Val Gly Val Ser Tyr Trp Lys Ser Ser
115 120 125

Glu Gly Ala Glu Tyr Asp Asp Gln Thr Ser Gln Arg Glu Lys Glu Asp
130 135 140

Asp Lys Val Phe Pro Gly Lys Ser His Thr Tyr Val Trp Gln Val Leu
145 150 155 160

Lys Glu Asn Gly Pro Thr Ala Ser Asp Pro Pro Cys Leu Thr Tyr Ser
165 170 175

Tyr Leu Ser His Val Asp Leu Val Lys Asp Leu Asn Ser Gly Leu Ile
180 185 190

Gly Ala Leu Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr
195 200 205

Gln Thr Leu His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly
210 215 220

Lys Ser Trp His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp
225 230 235 240

Ala Ala Ser Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr
245 250 255

Val Asn Arg Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val
260 265 270

Tyr Trp His Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile
275 280 285

Phe Leu Glu Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser
290 295 300

Leu Glu Ile Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met
305 310 315 320

Asp Leu Gly Gln Phe Leu Leu Ser Cys His Ile Ser Ser His Gln His
325 330 335

Asp Gly Met Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro
340 345 350

-continued

```
Gln Leu Arg Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp
        355                 360                 365

Leu Thr Asp Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser
    370                 375                 380

Pro Ser Phe Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr
385                 390                 395                 400

Trp Val His Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro
                405                 410                 415

Leu Val Leu Ala Pro Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn
            420                 425                 430

Asn Gly Pro Gln Arg Ile Gly Arg Lys Tyr Lys Lys Val Arg Phe Met
        435                 440                 445

Ala Tyr Thr Asp Glu Thr Phe Lys Thr Arg Glu Ala Ile Gln His Glu
    450                 455                 460

Ser Gly Ile Leu Gly Pro Leu Leu Tyr Gly Glu Val Gly Asp Thr Leu
465                 470                 475                 480

Leu Ile Ile Phe Lys Asn Gln Ala Ser Arg Pro Tyr Asn Ile Tyr Pro
                485                 490                 495

His Gly Ile Thr Asp Val Arg Pro Leu Tyr Ser Arg Arg Leu Pro Lys
            500                 505                 510

Gly Val Lys His Leu Lys Asp Phe Pro Ile Leu Pro Gly Glu Ile Phe
        515                 520                 525

Lys Tyr Lys Trp Thr Val Thr Val Glu Asp Gly Pro Thr Lys Ser Asp
    530                 535                 540

Pro Arg Cys Leu Thr Arg Tyr Tyr Ser Ser Phe Val Asn Met Glu Arg
545                 550                 555                 560

Asp Leu Ala Ser Gly Leu Ile Gly Pro Leu Leu Ile Cys Tyr Lys Glu
                565                 570                 575

Ser Val Asp Gln Arg Gly Asn Gln Ile Met Ser Asp Lys Arg Asn Val
            580                 585                 590

Ile Leu Phe Ser Val Phe Asp Glu Asn Arg Ser Trp Tyr Leu Thr Glu
        595                 600                 605

Asn Ile Gln Arg Phe Leu Pro Asn Pro Ala Gly Val Gln Leu Glu Asp
    610                 615                 620

Pro Glu Phe Gln Ala Ser Asn Ile Met His Ser Ile Asn Gly Tyr Val
625                 630                 635                 640

Phe Asp Ser Leu Gln Leu Ser Val Cys Leu His Glu Val Ala Tyr Trp
                645                 650                 655

Tyr Ile Leu Ser Ile Gly Ala Gln Thr Asp Phe Leu Ser Val Phe Phe
            660                 665                 670

Ser Gly Tyr Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr
        675                 680                 685

Leu Phe Pro Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro
    690                 695                 700

Gly Leu Trp Ile Leu Gly Cys His Asn Ser Asp Phe Arg Asn Arg Gly
705                 710                 715                 720

Met Thr Ala Leu Leu Lys Val Ser Ser Cys Asp Lys Asn Thr Gly Asp
                725                 730                 735

Tyr Tyr Glu Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys
            740                 745                 750

Asn Asn Ala Ile Glu Pro Arg Ser Phe Ser Gln Asn Pro Pro Val Leu
```

-continued

```
        755                 760                 765

Lys Arg His Gln Arg Glu Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln
    770                 775                 780

Glu Glu Ile Asp Tyr Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu
785                 790                 795                 800

Asp Phe Asp Ile Tyr Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe
                805                 810                 815

Gln Lys Lys Thr Arg His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp
            820                 825                 830

Asp Tyr Gly Met Ser Ser Ser Pro His Val Leu Arg Asn Arg Ala Gln
        835                 840                 845

Ser Gly Ser Val Pro Gln Phe Lys Lys Val Val Phe Gln Glu Phe Thr
    850                 855                 860

Asp Gly Ser Phe Thr Gln Pro Leu Tyr Arg Gly Glu Leu Asn Glu His
865                 870                 875                 880

Leu Gly Leu Leu Gly Pro Tyr Ile Arg Ala Glu Val Glu Asp Asn Ile
                885                 890                 895

Met Val Thr Phe Arg Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser
            900                 905                 910

Ser Leu Ile Ser Tyr Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg
        915                 920                 925

Lys Asn Phe Val Lys Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val
    930                 935                 940

Gln His His Met Ala Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp
945                 950                 955                 960

Ala Tyr Phe Ser Asp Val Asp Leu Glu Lys Asp Val His Ser Gly Leu
                965                 970                 975

Ile Gly Pro Leu Leu Val Cys His Thr Asn Thr Leu Asn Pro Ala His
            980                 985                 990

Gly Arg Gln Val Thr Val Gln Glu  Phe Ala Leu Phe Phe  Thr Ile Phe
        995                 1000                1005

Asp Glu  Thr Lys Ser Trp Tyr  Phe Thr Glu Asn Met  Glu Arg Asn
    1010                1015                1020

Cys Arg  Ala Pro Cys Asn Ile  Gln Met Glu Asp Pro  Thr Phe Lys
    1025                1030                1035

Glu Asn  Tyr Arg Phe His Ala  Ile Asn Gly Tyr Ile  Met Asp Thr
    1040                1045                1050

Leu Pro  Gly Leu Val Met Ala  Gln Asp Gln Arg Ile  Arg Trp Tyr
    1055                1060                1065

Leu Leu  Ser Met Gly Ser Asn  Glu Asn Ile His Ser  Ile His Phe
    1070                1075                1080

Ser Gly  His Val Phe Thr Val  Arg Lys Lys Glu Glu  Tyr Lys Met
    1085                1090                1095

Ala Leu  Tyr Asn Leu Tyr Pro  Gly Val Phe Glu Thr  Val Glu Met
    1100                1105                1110

Leu Pro  Ser Lys Ala Gly Ile  Trp Arg Val Glu Cys  Leu Ile Gly
    1115                1120                1125

Glu His  Leu His Ala Gly Met  Ser Thr Leu Phe Leu  Val Tyr Ser
    1130                1135                1140

Asn Lys  Cys Gln Thr Pro Leu  Gly Met Ala Ser Gly  His Ile Arg
    1145                1150                1155
```

-continued

```
Asp Phe  Gln Ile Thr Ala Ser  Gly Gln Tyr Gly Gln  Trp Ala Pro
    1160                 1165                 1170

Lys Leu  Ala Arg Leu His Tyr  Ser Gly Ser Ile Asn  Ala Trp Ser
    1175                 1180                 1185

Thr Lys  Glu Pro Phe Ser Trp  Ile Lys Val Asp Leu  Leu Ala Pro
    1190                 1195                 1200

Met Ile  Ile His Gly Ile Lys  Thr Gln Gly Ala Arg  Gln Lys Phe
    1205                 1210                 1215

Ser Ser  Leu Tyr Ile Ser Gln  Phe Ile Ile Met Tyr  Ser Leu Asp
    1220                 1225                 1230

Gly Lys  Lys Trp Gln Thr Tyr  Arg Gly Asn Ser Thr  Gly Thr Leu
    1235                 1240                 1245

Met Val  Phe Phe Gly Asn Val  Asp Ser Ser Gly Ile  Lys His Asn
    1250                 1255                 1260

Ile Phe  Asn Pro Pro Ile Ile  Ala Arg Tyr Ile Arg  Leu His Pro
    1265                 1270                 1275

Thr His  Tyr Ser Ile Arg Ser  Thr Leu Arg Met Glu  Leu Met Gly
    1280                 1285                 1290

Cys Asp  Leu Asn Ser Cys Ser  Met Pro Leu Gly Met  Glu Ser Lys
    1295                 1300                 1305

Ala Ile  Ser Asp Ala Gln Ile  Thr Ala Ser Ser Tyr  Phe Thr Asn
    1310                 1315                 1320

Met Phe  Ala Thr Trp Ser Pro  Ser Lys Ala Arg Leu  His Leu Gln
    1325                 1330                 1335

Gly Arg  Ser Asn Ala Trp Arg  Pro Gln Val Asn Asn  Pro Lys Glu
    1340                 1345                 1350

Trp Leu  Gln Val Asp Phe Gln  Lys Thr Met Lys Val  Thr Gly Val
    1355                 1360                 1365

Thr Thr  Gln Gly Val Lys Ser  Leu Leu Thr Ser Met  Tyr Val Lys
    1370                 1375                 1380

Glu Phe  Leu Ile Ser Ser Ser  Gln Asp Gly His Gln  Trp Thr Leu
    1385                 1390                 1395

Phe Phe  Gln Asn Gly Lys Val  Lys Val Phe Gln Gly  Asn Gln Asp
    1400                 1405                 1410

Ser Phe  Thr Pro Val Val Asn  Ser Leu Asp Pro Pro  Leu Leu Thr
    1415                 1420                 1425

Arg Tyr  Leu Arg Ile His Pro  Gln Ser Trp Val His  Gln Ile Ala
    1430                 1435                 1440

Leu Arg  Met Glu Val Leu Gly  Cys Glu Ala Gln Asp  Leu Tyr
    1445                 1450                 1455


<210> SEQ ID NO 108
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 108

atgcagattg agctgtccac ctgcttcttt ctgtgcctgc tgagattctg cttctctgcc     60

accaggagat actacctggg ggctgtggaa ctttcttggg actacatgca gtctgacctg    120
```

-continued

ggagagctgc ctgtggatgc caggttccca cccagagtgc ccaagtcctt cccattcaac 180

acctctgtgg tctacaagaa gacactcttt gtggaattca ctgaccacct gttcaacatt 240

gcaaaaccca gaccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcgtcaccct caagaacatg gcatcccacc ctgtgtctct gcatgctgtg 360

ggagtctcat actggaaatc ctctgaaggg gctgagtatg atgaccagac atcccagaga 420

gagaaagagg atgacaaggt gttccctggg aagtctcaca cctatgtgtg gcaagtcctc 480

aaggagaatg gacccactgc atctgaccca ccctgcctga catactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg cactgctggt gtgcagggaa 600

ggatccctgg ccaaggagaa aacccagaca ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagtcttg gcactctgaa acaaagaact ccctgatgca agacagggat 720

gctgcctctg ccagggcatg gcccaagatg cacactgtga atggctatgt gaacagatca 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aagtgcactc catttttcctg gagggacaca ccttcctggt caggaaccac 900

agacaagcct ctctggagat ctctcccatc accttcctca ctgcacagac actgctgatg 960

gaccttggac agttcctgct gtcctgccac atctcttccc accagcatga tggcatggaa 1020

gcctatgtca aggtggactc atgccctgag gaaccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt cagatttgat 1140

gatgacaact ctccatcctt cattcagatc aggtctgtgg caaagaaaca ccccaagaca 1200

tgggtgcact acattgctgc tgaggaagag gactgggact atgcaccact ggtcctggcc 1260

cctgatgaca ggagctacaa gtctcagtac ctcaacaatg gcccacaaag aattggaaga 1320

aagtacaaga aagtcagatt catggcctac actgatgaaa ccttcaagac aagagaagcc 1380

attcagcatg agtctggcat tctgggacca ctcctgtatg gggaagtggg agacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag caggagactg ccaaaagggg tgaaacacct caaggacttc 1560

cccattctgc ctggagagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

acaaagtctg accccaggtg cctcaccaga tactactcct cttttgtgaa catggagaga 1680

gacctggcat ctggactgat tggaccactg ctcatctgct acaaggagtc tgtggaccag 1740

agaggcaacc agatcatgtc tgacaagaga aatgtgattc tgttctctgt ctttgatgag 1800

aacagatcat ggtacctgac tgagaacatt cagagattcc tgcccaaccc tgctggggtg 1860

caactggaag accctgagtt ccaggcaagc aacatcatgc actccatcaa tggctatgtg 1920

tttgactctc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggcac aaactgactt cctttctgtc ttcttctctg gatacacctt caagcacaag 2040

atggtgtatg aggacaccct gacactcttc ccattctctg gggaaactgt gttcatgagc 2100

atggagaacc ctggactgtg gattctggga tgccacaact ctgacttcag aaacagggga 2160

atgactgcac tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

tcttatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccagaagc 2280

ttctctcaga atccacctgt cctgaagaga caccagagag agatcaccag gacaaccctc 2340

cagtctgacc aggaagagat tgactatgat gacaccattt ctgtggagat gaagaaggag 2400

-continued

gactttgaca tctatgatga ggacgagaac cagtctccaa gatcattcca gaagaagaca 2460

agacactact tcattgctgc tgtggaaaga ctgtgggact atggcatgtc ttcctctccc 2520

catgtcctca ggaacagggc acagtctggc tctgtgccac agttcaagaa agtggtcttc 2580

caggagttca ctgatggctc attcacccag cccctgtaca gaggggaact gaatgagcac 2640

ctgggactcc tgggaccata catcagggct gaggtggaag acaacatcat ggtgacattc 2700

agaaaccagg cctccaggcc ctacagcttc tactcttccc tcatcagcta tgaggaagac 2760

cagagacaag gggctgagcc aagaaagaac tttgtgaaac ccaatgaaac caagacctac 2820

ttctggaaag tccagcacca catggcaccc accaaggatg agtttgactg caaggcctgg 2880

gcatacttct ctgatgtgga cctggagaaa gatgtgcact ctggcctgat tggcccactc 2940

ctggtctgcc acaccaacac cctgaaccct gcacatggaa ggcaagtgac tgtgcaggag 3000

tttgccctct tcttcaccat ctttgatgaa accaagtcat ggtacttcac tgagaacatg 3060

gagagaaact gcagagcacc atgcaacatt cagatggaag accccacctt caaggagaac 3120

tacaggttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggca 3180

caggaccaga gaatcagatg gtacctgctt tctatgggat ccaatgagaa cattcactcc 3240

atccacttct ctgggcatgt cttcactgtg agaaagaagg aggaatacaa gatggccctg 3300

tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc 3360

tggagggtgg aatgcctcat tggggagcac ctgcatgctg gcatgtcaac cctgttcctg 3420

gtctacagca acaagtgcca gacacccctg ggaatggcct ctggccacat cagggacttc 3480

cagatcactg cctctggcca gtatggccag tgggcaccca aactggccag gctccactac 3540

tctggctcca tcaatgcatg gtcaaccaag gagccattct cttggatcaa ggtggacctg 3600

ctggcaccca tgatcattca tggcatcaag acacaggggg caagacagaa attctcctct 3660

ctgtacatct cacagttcat catcatgtac tctctggatg gcaagaagtg gcagacatac 3720

agaggcaact ccactggcac cctcatggtc ttctttggca atgtggacag ctctggcatc 3780

aagcacaaca tcttcaaccc tcccatcatt gccagataca tcaggctgca ccccacccac 3840

tactcaatca gatcaaccct caggatggaa ctgatgggat gtgacctgaa ctcctgctca 3900

atgcccctgg gaatggagag caaggccatt tctgatgccc agatcactgc atcctcttac 3960

ttcaccaaca tgtttgccac ctggtcacca tcaaaagcca ggctgcacct ccagggaaga 4020

agcaatgcct ggagacccca ggtcaacaac ccaaaggaat ggctgcaagt ggacttccag 4080

aagacaatga aagtcactgg ggtgacaacc caggggtca agtctctgct cacctcaatg 4140

tatgtgaagg agttcctgat ctcttcctca caggatggcc accagtggac actcttcttc 4200

cagaatggca aagtcaaggt gttccagggc aaccaggact ctttcacacc tgtggtgaac 4260

tcactggacc ccccctcct gacaagatac ctgagaattc acccccagtc ttgggtccac 4320

cagattgccc tgagaatgga agtcctggga tgtgaggcac aagacctgta ctga 4374

<210> SEQ ID NO 109
<211> LENGTH: 4374
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 109

-continued

atgcagattg agctgagcac ctgcttcttc ctgtgcctgc tgaggttctg cttctctgcc 60

accaggagat actacctggg ggctgtggag ctttcttggg actacatgca gtctgacctg 120

ggggagctgc ctgtggatgc caggttccca cccagagtgc ccaaatcctt cccattcaac 180

acctctgtgg tctacaagaa gaccctcttt gtggagttca ctgaccacct gttcaacatt 240

gccaaaccca ggccaccctg gatgggactc ctgggaccca ccattcaggc tgaggtgtat 300

gacactgtgg tcgtcaccct caagaacatg gcctcccacc ctgtgagcct gcatgctgtg 360

ggggtcagct actggaagtc ctctgagggg gctgagtatg atgaccagac ctcccagagg 420

gagaaggagg atgacaaagt gttccctggg aagagccaca cctatgtgtg gcaggtcctc 480

aaggagaatg gccccactgc ctctgaccca ccctgcctga cctactccta cctttctcat 540

gtggacctgg tcaaggacct caactctgga ctgattgggg ccctgctggt gtgcagggag 600

ggctccctgg ccaaagagaa gacccagacc ctgcacaagt tcattctcct gtttgctgtc 660

tttgatgagg gcaagagctg gcactctgaa accaagaact ccctgatgca ggacagggat 720

gctgcctctg ccagggcctg gcccaagatg cacactgtga atggctatgt gaacaggagc 780

ctgcctggac tcattggctg ccacaggaaa tctgtctact ggcatgtgat tggcatgggg 840

acaacccctg aggtgcactc cattttcctg gagggccaca ccttcctggt caggaaccac 900

agacaggcca gcctggagat cagccccatc accttcctca ctgcccagac cctgctgatg 960

gacctcggac agttcctgct gtcctgccac atcagctccc accagcatga tggcatggag 1020

gcctatgtca aggtggacag ctgccctgag gagccacagc tcaggatgaa gaacaatgag 1080

gaggctgagg actatgatga tgacctgact gactctgaga tggatgtggt ccgctttgat 1140

gatgacaaca gcccatcctt cattcagatc aggtctgtgg ccaagaaaca ccccaagacc 1200

tgggtgcact acattgctgc tgaggaggag gactgggact atgccccact ggtcctggcc 1260

cctgatgaca ggagctacaa gagccagtac ctcaacaatg gcccacagag gattggacgc 1320

aagtacaaga aagtcaggtt catggcctac actgatgaaa ccttcaagac cagggaggcc 1380

attcagcatg agtctggcat cctgggccca ctcctgtatg gggaggtggg ggacaccctg 1440

ctcatcatct tcaagaacca ggcctccagg ccctacaaca tctacccaca tggcatcact 1500

gatgtcaggc ccctgtacag ccgcaggctg ccaaaggggg tgaaacacct caaggacttc 1560

cccattctgc ctggggagat cttcaagtac aagtggactg tcactgtgga ggatggacca 1620

accaaatctg accccaggtg cctcaccaga tactactcca gctttgtgaa catggagagg 1680

gacctggcct ctggcctgat tggcccactg ctcatctgct acaaggagtc tgtggaccag 1740

aggggaaacc agatcatgtc tgacaagagg aatgtgattc tgttctctgt ctttgatgag 1800

aacaggagct ggtacctgac tgagaacatt cagcgcttcc tgcccaaccc tgctggggtg 1860

cagctggagg accctgagtt ccaggccagc aacatcatgc actccatcaa tggctatgtg 1920

tttgacagcc tccagctttc tgtctgcctg catgaggtgg cctactggta cattctttct 1980

attggggccc agactgactt cctttctgtc ttcttctctg gctacacctt caaacacaag 2040

atggtgtatg aggacaccct gaccctcttc ccattctctg gggagactgt gttcatgagc 2100

atggagaacc ctggcctgtg gattctggga tgccacaact ctgacttccg caacaggggc 2160

atgactgccc tgctcaaagt ctcctcctgt gacaagaaca ctggggacta ctatgaggac 2220

agctatgagg acatctctgc ctacctgctc agcaagaaca atgccattga gcccaggagc 2280

-continued

ttcagccaga atccacctgt cctgaaacgc caccagaggg agatcaccag gaccaccctc 2340

cagtctgacc aggaggagat tgactatgat gacaccattt ctgtggagat gaagaaagag 2400

gactttgaca tctatgacga ggacgagaac cagagcccaa ggagcttcca gaagaagacc 2460

aggcactact tcattgctgc tgtggagcgc ctgtgggact atggcatgag ctccagcccc 2520

catgtcctca ggaacagggc ccagtctggc tctgtgccac agttcaagaa agtggtcttc 2580

caagagttca ctgatggcag cttcacccag cccctgtaca gaggggagct gaatgagcac 2640

ctgggactcc tgggcccata catcagggct gaggtggagg acaacatcat ggtgaccttc 2700

cgcaaccagg cctccaggcc ctacagcttc tacagctccc tcatcagcta tgaggaggac 2760

cagaggcagg gggctgagcc acgcaagaac tttgtgaaac ccaatgaaac caagacctac 2820

ttctggaaag tccagcacca catggccccc accaaggatg agtttgactg caaggcctgg 2880

gcctacttct ctgatgtgga cctggagaag gatgtgcact ctggcctgat tggcccactc 2940

ctggtctgcc acaccaacac cctgaaccct gcccatggaa ggcaagtgac tgtgcaggag 3000

tttgccctct tcttcaccat ctttgatgaa accaagagct ggtacttcac tgagaacatg 3060

gagcgcaact gcagggcccc atgcaacatt cagatggagg accccacctt caaagagaac 3120

taccgcttcc atgccatcaa tggctacatc atggacaccc tgcctgggct tgtcatggcc 3180

caggaccaga ggatcaggtg gtacctgctt tctatgggct ccaatgagaa cattcactcc 3240

atccacttct ctgggcatgt cttcactgtg cgcaagaagg aggagtacaa gatggccctg 3300

tacaacctct accctggggt ctttgagact gtggagatgc tgccctccaa agctggcatc 3360

tggagggtgg agtgcctcat tggggagcac ctgcatgctg gcatgagcac cctgttcctg 3420

gtctacagca acaagtgcca gacccccctg ggaatggcct ctggccacat cagggacttc 3480

cagatcactg cctctggcca gtatggccag tgggccccca agctggccag gctccactac 3540

tctggatcca tcaatgcctg gagcaccaag gagccattca gctggatcaa agtggacctg 3600

ctggccccca tgatcatcca tggcatcaag acccaggggg ccaggcagaa gttctccagc 3660

ctgtacatca gccagttcat catcatgtac agcctggatg gcaagaaatg gcagacctac 3720

agaggcaact ccactggaac actcatggtc ttctttggca atgtggacag ctctggcatc 3780

aagcacaaca tcttcaaccc cccaatcatc gccagataca tcaggctgca ccccacccac 3840

tacagcatcc gcagcaccct caggatggag ctgatgggct gtgacctgaa ctcctgcagc 3900

atgcccctgg gcatggagag caaggccatt tctgatgccc agatcactgc ctccagctac 3960

ttcaccaaca tgtttgccac ctggagccca agcaaggcca ggctgcacct ccagggaagg 4020

agcaatgcct ggaggcccca ggtcaacaac ccaaaggagt ggctgcaggt ggacttccag 4080

aagaccatga aggtcactgg ggtgaccacc caggggtca agagcctgct caccagcatg 4140

tatgtgaagg agttcctgat cagctccagc caggatggcc accagtggac cctcttcttc 4200

cagaatggca aggtcaaggt gttccagggc aaccaggaca gcttcacccc tgtggtgaac 4260

agcctggacc ccccctcct gaccagatac ctgaggattc acccccagag ctgggtccac 4320

cagattgccc tgaggatgga ggtcctggga tgtgaggccc aggacctgta ctga 4374

1-74. (canceled)

75. A polynucleotide comprising a nucleotide sequence encoding a Factor VIII polypeptide, the Factor VIII polypeptide comprising a light chain, a heavy chain, and a polypeptide linker joining the C-terminus of the heavy chain to the N-terminus of the light chain,

wherein the heavy chain of the Factor VIII polypeptide comprises a first polypeptide sequence having at least 95% identity to amino acids 20 to 759 of SEQ ID NO: 2;

wherein the light chain of the Factor FVIII polypeptide comprises a second polypeptide sequence having at least 95% identity to nucleic acids 774 to 1457 of SEQ ID NO: 2; and

wherein the polypeptide linker comprises a furin cleavage site and a glycosylation peptide having an amino acid sequence of SEQ ID NO: 55.

76. The polynucleotide of claim **75**, wherein the encoded Factor VIII polypeptide comprises I105V, A127S, G151K, M166T, and L171P amino acid substitutions, relative to SEQ ID NO: 19.

77. The polynucleotide of claim **75**, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO:113.

78. The polynucleotide of claim **75**, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO:113.

79. The polynucleotide of claim **75**,

wherein the heavy chain of the Factor VIII polypeptide comprises a first polypeptide sequence having at least 99% identity to amino acids 20 to 759 of SEQ ID NO: 2;

wherein the light chain of the Factor FVIII polypeptide comprises a second polypeptide sequence having at least 99% identity to nucleic acids 774 to 1457 of SEQ ID NO: 2.

80. The polynucleotide of claim **79**, wherein the encoded Factor VIII polypeptide comprises I105V, A127S, G151K, M166T, and L171P amino acid substitutions, relative to SEQ ID NO: 19.

81. The polynucleotide of claim **79**, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO:113.

82. The polynucleotide of claim **80**, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO:113.

83. The polynucleotide of claim **75**, wherein the encoded Factor VIII polypeptide comprises a sequence having at least 99% sequence identity to SEQ ID NO: 2.

84. The polynucleotide of claim **83**, wherein the encoded Factor VIII polypeptide comprises I105V, A127S, G151K, M166T, and L171P amino acid substitutions, relative to SEQ ID NO: 19.

85. The polynucleotide of claim **83**, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO:113.

86. The polynucleotide of claim **84**, wherein the polypeptide linker comprises an amino acid sequence of SEQ ID NO:113.

87. The polynucleotide of claim **75**, further comprising a promoter element operably linked to the polynucleotide encoding the Factor VIII polypeptide.

88. The polynucleotide of claim **87**, wherein the promoter element is a liver-specific promoter sequence upstream of the nucleotide sequence encoding the Factor VIII polypeptide.

89. An adeno-associated virus (AAV) vector comprising a polynucleotide according to claim **75**.

90. An adeno-associated virus (AAV) particle comprising a polynucleotide according to claim **75**.

91. The adeno-associated virus (AAV) particle according to claim **90**, wherein the AAV particle is an AAV-8 particle.

92. A host cell infected with an adeno-associated virus (AAV) particle comprising a polynucleotide according to claim **75**.

93. A method for producing an adeno-associated virus (AAV) particle comprising introducing a polynucleotide according to claim **75** into a mammalian host cell, wherein the polynucleotide is competent for replication in the mammalian host cell.

94. A method for treating hemophilia A comprising administering, to a patient in need thereof, an adeno-associated virus (AAV) particle according to claim **90**.

* * * * *