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(54) **METHODS OF REVERSING CACHEXIA AND PROLONGING SURVIVAL COMPRISING ADMINISTERING A GDF15 MODULATOR AND AN ANTI-CANCER AGENT**

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(57) **ABSTRACT**

Methods are provided for improved treatment of subjects with cancer anorexia-cachexia syndrome, comprising treatment with a combination of at least one anti-cancer agent and at least one GDF 15 modulator. Methods are further provided for improved treatment of subjects with anti-cancer agents which induce cachexia, comprising further treating the subject with at least one GDF 15 modulator.

FIGURE 1 Inhibition of GDF15 Significantly Improved Overall Survival in Cancer Cachexia Tumor Bearing Mice

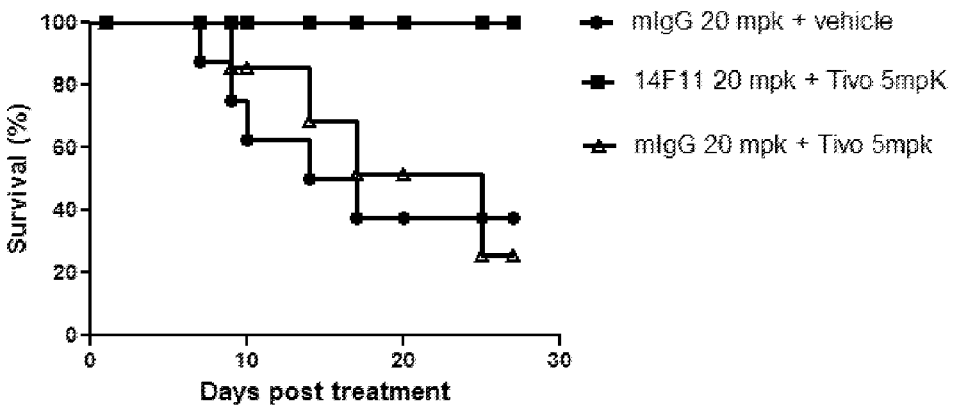
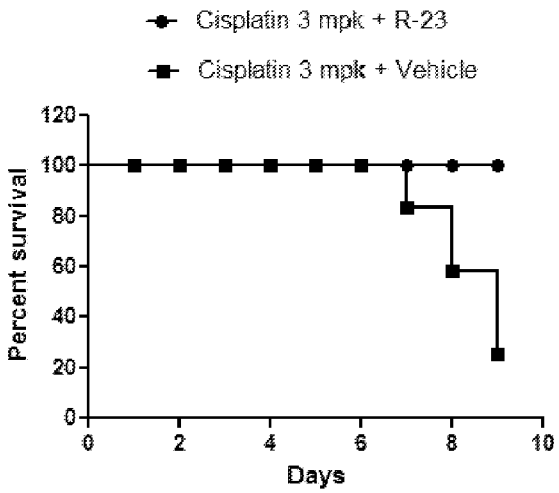


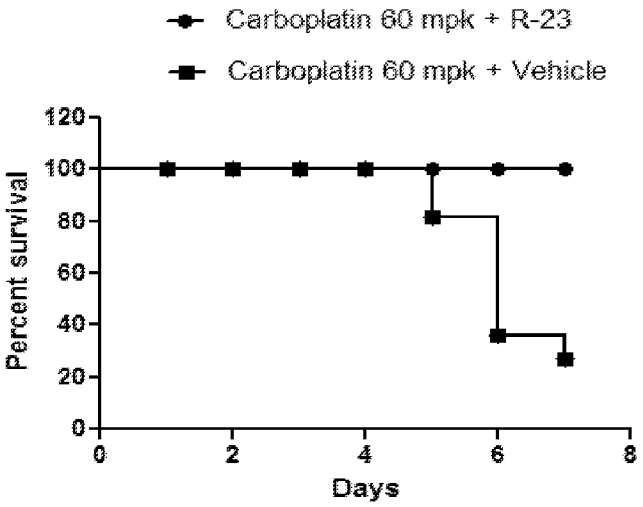
FIGURE 2 Inhibition of GDF15 Significantly Improved Overall Survival in Cisplatin-induced Cachexia Model



Survival criteria:
1. Alive
2. Body weight loss <20%
3. Better than moribund health

HR: 0.09 P: 0.001

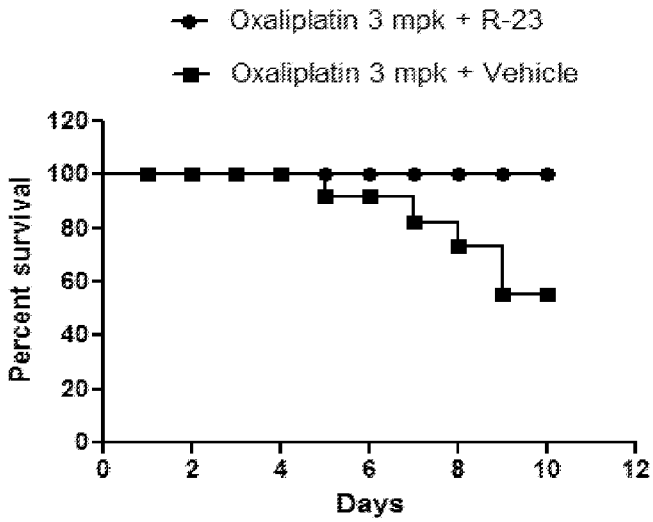
FIGURE 3: Inhibition of GDF15 Significantly Improved Overall Survival in Carboplatin-induced Cachexia Model



Survival criteria:
1. Alive
2. Body weight loss <20%
3. Better than moribund health

HR: 0.09 P: 0.02

FIGURE 4: Inhibition of GDF15 Significantly Improved Overall Survival in Oxaliplatin-induced Cachexia Model



Survival criteria:
1. Alive
2. Body weight loss <20%
3. Better than moribund health

HR: 0.12 P: 0.024

METHODS OF REVERSING CACHEXIA AND PROLONGING SURVIVAL COMPRISING ADMINISTERING A GDF15 MODULATOR AND AN ANTI-CANCER AGENT

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 62/055,203, filed Sep. 25, 2014, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] A large majority of advanced cancer patients experience progressive weight loss associated with anorexia, malnutrition, anemia, inflammation and suppression of immune functions. Collectively, this series of complex and inter-related symptoms have been described as Cancer Anorexia-Cachexia Syndrome (CACS). CACS is associated with muscle and fat mass loss, decreased quality of life, reduced response to anti-cancer therapies, increased treatment toxicity and reduced survival. Further, certain chemotherapeutic treatments used to treat various cancers have been shown to induce or contribute to cachexia. In particular, subjects treated with platinum-based therapies, such as carboplatin and oxaliplatin, may experience dose-limiting, harmful, and sometimes fatal cachexia.

[0003] Growth Differentiation Factor-15 (GDF15) is a member of the transforming growth factor-beta (TGF-β) superfamily of proteins, which comprise a large group of multifunctional proteins that serve as regulators of cell proliferation and differentiation. Prominent members of this family include the TGF-βs 1-5, activins, bone morphogenetic proteins (BMPs) that serve as regulators of bone, cartilage and other tissue types, and other proteins involved in cellular regulation, such as glial cell-line derived neurotrophic factor (GDNF), and myostatin (also known as GDF-8). GDF15 was isolated early on from such tissues as prostate and placenta, and has been known by the additional names macrophage inhibitory cytokine 1 (or MIC1), NSAID-activated gene 1 protein (or NAG1), NSAID-regulated gene 1 protein (or NRG-1), placental TGF-beta (or PTGFB), placental bone morphogenetic protein (or PLAB), and prostate differentiation factor (or PDF).

[0004] Monoclonal antibodies against GDF15 have been recognized as potential anti-cachexia therapeutic agents. See, e.g., U.S. Pat. No. 8,192,735 and WO 2014/100689.

SUMMARY OF THE INVENTION

[0005] The present inventors have discovered that, among other things, inhibition of GDF15 can reverse chemotherapy-induced cachexia. Accordingly, inhibition of GDF15 allows enhanced treatment by reducing the dose-limiting cachexia caused by such chemotherapeutics. The present inventors have also discovered that prevention and/or reversal of cachexia by administration of a GDF15 modulator is useful for the increase of overall survival in subjects treated with anti-cancer agents. Additionally, the inventors have discovered that treatment of cachexia can be integrated into anti-cancer treatment regimens to increase the therapeutic benefit.

[0006] In one aspect, the disclosure relates to a method for increasing the overall survival in a subject having cancer anorexia-cachexia syndrome, comprising treating the subject with at least one anti-cancer agent and at least one GDF15 modulator.

[0007] In another aspect, the disclosure relates to a method for increasing the overall survival in a subject being treated with an anti-cancer agent, comprising further treating the subject with at least one GDF15 modulator. In certain embodiments, the anti-cancer agent induces cachexia.

[0008] In another aspect, the disclosure relates to a method for increasing the overall survival in a subject bearing a cachexia-inducing tumor, comprising treating the subject with at least one anti-cancer agent and at least one GDF15 modulator.

[0009] In another aspect, the disclosure relates to a method of treating a subject with cancer anorexia-cachexia syndrome, the method comprising administering a GDF15 modulator and an anti-cancer agent, wherein administration of the GDF15 modulator and the anti-cancer agent prolongs mean survival in a first patient population with cancer anorexia-cachexia syndrome relative to a second patient population with cancer anorexia-cachexia syndrome who do not receive the GDF15 modulator.

[0010] In certain embodiments of any of the methods disclosed herein, the anti-cancer agent is selected from the group consisting of: capecitabine, gemcitabine, doxorubicin, cisplatin, carboplatin and oxaliplatin. In certain embodiments, the GDF15 modulator is an anti-GDF15 antibody, or a GDF15-binding fragment thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0011] FIG. **1** shows a graph illustrating the effects of treatment with GDF15 inhibitory antibody on survival of mice with tumors.

[0012] FIG. **2** shows a graph illustrating the effects of combined treatment with cisplatin and a GDF15 inhibitory antibody on chemotherapy-induced cachexia in mice.

[0013] FIG. **3** shows a graph illustrating the effects of combined treatment with carboplatin and a GDF15 inhibitory antibody on chemotherapy-induced cachexia in mice.

[0014] FIG. **4** shows a graph illustrating the effects of combined treatment with oxaliplatin and a GDF15 inhibitory antibody on chemo-induced cachexia in mice.

DETAILED DESCRIPTION

I. GDF15 Modulators

[0015] As used herein a "GDF15 modulator" is understood to mean an agent that reduces or inhibits GDF15 activity or the activity of the GDF15 pathway, which can result from reduced expression, amount, or biological activity or function, of GDF15 or the GDF15 pathway. GDF15 modulators or modulating agents useful in the practice of the invention may comprise an anti-GDF15 antibody, an anti-GDF15 receptor antibody, soluble GDF15 mimetics or analogs that prevent GDF15 from binding to its cognate binding partner, a soluble GDF15 receptor mimetic or analog that prevents GDF15 from binding to its cognate binding partner. Additional exemplary GDF15 modulating agents include small molecule inhibitors of GDF15 or a GDF15 receptor, interfering nucleic acids (for example, interfering RNA or antisense nucleic acids, such as antisense DNA or RNA) that interfere with expression of endogenous GDF15 or a cognate receptor.

[0016] Antibodies against GDF15, GDF15-binding fragments thereof, and methods for their use have been described in U.S. Pat. No. 8,192,735; WO 2014/100689 (corresponding to U.S. Patent Publication No. US 2014-0193427-A1); and International Patent Application Nos. PCT/US2015/036790 and PCT/US2015/036794. These documents are hereby incorporated herein in their entirety, including their description of GDF15, GDF15 modulators (e.g., GDF15 inhibitors), antibodies to GDF15, methods of producing and using such modulators and antibodies, as well as their description of compositions, formulations, excipients and carriers, therapeutically effective amounts, dosage forms and modes of administration.

[0017] In a preferred embodiment, the GDF15 modulating agent can comprise an anti-GDF15 antibody, which is humanized or human. As used herein, unless otherwise indicated, the term "antibody" is understood to mean an intact antibody (e.g., an intact monoclonal antibody) or antigen-binding fragment of an antibody, including an intact antibody or antigen-binding fragment of an antibody (e.g., a phage display antibody including a fully human antibody, a semisynthetic antibody or a fully synthetic antibody) that has been optimized, engineered or chemically conjugated. Examples of antibodies that have been optimized are affinity-matured antibodies. Examples of antibodies that have been engineered are Fc optimized antibodies, and multispecific antibodies (e.g., bispecific antibodies). Examples of antigen-binding fragments include Fab, Fab', $F(ab')_2$, Fv, single chain antibodies (e.g., scFv), minibodies and diabodies. An antibody conjugated to a toxin moiety is an example of a chemically conjugated antibody.

[0018] In certain embodiments, the antibody comprises: (a) an immunoglobulin heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3} and (b) an immunoglobulin light chain variable region, wherein the heavy chain variable region and the light chain variable region together define a single binding site for binding GDF15 or a GDF15 receptor. The CDR_{H1}, CDR_{H2}, and CDR_{H3} sequences are interposed between immunoglobulin framework (FR) sequences. In certain other embodiments, the antibody comprises (a) an immunoglobulin light chain variable region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3}, and (b) an immunoglobulin heavy chain variable region, wherein the IgG light chain variable region and the IgG heavy chain variable region together define a single binding site for binding GDF15 or a GDF15 receptor. The CDR_{L1}, CDR_{L2}, and CDR_{L3} sequences are interposed between immunoglobulin FR sequences. In certain other embodiments, the antibody comprises: (a) an immunoglobulin heavy chain variable region comprising the structure CDR_{H1}-CDR_{H2}-CDR_{H3} and (b) an immunoglobulin light chain variable region comprising the structure CDR_{L1}-CDR_{L2}-CDR_{L3}, wherein the heavy chain variable region and the light chain variable region together define a single binding site for binding GDF15 or a GDF15 receptor. Exemplary anti-GDF15 antibodies are described, for example, in U.S. Patent Publication No. US 2014-0193427-A1, the disclosure of which is incorporated by reference herein for all purposes.

[0019] Exemplary anti-GDF15 antibodies useful in the methods and compositions of the invention may, for example, include a heavy chain variable region comprising any one of the nine sets of CDR_{H1}, CDR_{H2}, and CDR_{H3} region sequences set forth in Table 1 below.

TABLE 1

	CDR_{H1}	CDR_{H2}	CDR_{H3}
1	DYNMD (SEQ ID NO: 1)	QINPNNGGIFFNQKFKG (SEQ ID NO: 4)	EAITTVGAMDY (SEQ ID NO: 13)
2	DYNMD (SEQ ID NO: 1)	QINPNNGGIFFNQKFQG (SEQ ID NO: 5)	EAITTVGAMDY (SEQ ID NO: 13)
3	DYNMD (SEQ ID NO: 1)	QINPYNHLIFFNQKFQG (SEQ ID NO: 6)	EAITTVGAMDY (SEQ ID NO: 13)
4	DYNMD (SEQ ID NO: 1)	QINPNNGLIFFNQKFQG (SEQ ID NO: 7)	EAITTVGAMDY (SEQ ID NO: 13)
5	DYNMD (SEQ ID NO: 1)	QINPNNGLIFFNQKFKG (SEQ ID NO: 8)	EAITTVGAMDY (SEQ ID NO: 13)
6	DYNMD (SEQ ID NO: 1)	QINPYNHLIFFNQKFKG (SEQ ID NO: 9)	EAITTVGAMDY (SEQ ID NO: 13)
7	TYGMGVS (SEQ ID NO: 2)	HIYWDDDKRYNPSLKS (SEQ ID NO: 10	RGYDDYWGY (SEQ ID NO: 14)
8	TYGMGVS (SEQ ID NO: 2)	HIYWDDDKRYNPSLKT (SEQ ID NO: 11)	RGYDDYWGY (SEQ ID NO: 14)
9	TYGMGVG (SEQ ID NO: 3)	DIW-WDDDKYYNPSLKS (SEQ ID NO: 12)	RGHYSAMDY (SEQ ID NO: 15)

[0020] Exemplary anti-GDF15 antibodies useful in the methods and compositions of the invention may, for example, include a light chain variable region comprising any one of the four sets of CDR_{L1}, CDR_{L2}, and CDR_{L3} region sequences set forth in Table 2 below.

TABLE 2

	$CDRL_1$	$CDRL_2$	$CDRL_1$
1	RTSENLHNYLA (SEQ ID NO: 16)	DAKTLAD (SEQ ID NO: 18)	QHFWSSPYT (SEQ ID NO: 21)
2	RTSENLHNYLA (SEQ ID NO: 16)	DAKTLAD (SEQ ID NO: 18)	QHFWSDPYT (SEQ ID NO: 22)
3	KASQNVGTNVA (SEQ ID NO: 17)	SASYRYS (SEQ ID NO: 19)	QQYNNYPLT (SEQ ID NO: 23)
4	KASQNVGTNVA (SEQ ID NO: 17)	SPSYRYS (SEQ ID NO: 20)	QQYNSYPHT (SEQ ID NO: 24)

[0021] Exemplary anti-GDF15 antibodies useful in the practice of the invention are described in U.S. Patent Publication No. US 2014-0193427-A1, including 01G06, 03G05, 04F08, 06C11, 08G01, 14F11, 17B11, as well as human or humanized forms thereof. In certain embodiments, the antibodies disclosed herein (e.g., 01G06, 03G05, 04F08, 06C11, 08G01, 14F11, or 17B11, or humanized forms thereof) are used to treat a subject with cancer anorexia-cachexia syndrome, wherein administration of the antibody and an anti-cancer agent prolongs mean survival in a first patient population with cancer anorexia-cachexia syndrome relative to a second patient population with cancer anorexia-cachexia syndrome who do not receive the GDF15 modulator.

[0022] In a preferred embodiment, an anti-GDF15 antibody useful in the practice of the invention is referred to as 01G06 in U.S. patent application Ser. No. 14/137,415. Humanized forms of the 01G06 antibody are listed below together with the amino acid sequences of their respective heavy and light chain variable regions. Exemplary humanized anti-GDF15 antibodies include: Hu01G06-1; Hu01G06-46; Hu01G06-52; Hu01G06-100; Hu01G06-101; Hu01G06-102; Hu01G06-103; Hu01G06-104; Hu01G06-105; Hu01G06-106; Hu01G06-107; Hu01G06-108; Hu01G06-109; Hu01G06-110; Hu01G06-111; Hu01G06-112; Hu01G06-113; Hu01G06-114; Hu01G06-122; Hu01G06-127; Hu01G06-135; Hu01G06-138; Hu01G06-146; Hu06C11-1; Hu06C11-27; Hu06C11-30; Hu14F11-1; Hu14F11-23; Hu14F11-24; Hu14F11-39; and Hu14F11-47. The amino acid sequences for the heavy chain and light chain for each of the aforementioned antibodies is set forth below in Table 3.

TABLE 3

Antibody Name	Light Chain	Heavy Chain
01G06 (murine)	SEQ ID NO: 25	SEQ ID NO: 37
Hu01G06-1	SEQ ID NO: 26	SEQ ID NO: 38
Hu01G06-46	SEQ ID NO: 27	SEQ ID NO: 39
Hu01G06-52	SEQ ID NO: 27	SEQ ID NO: 40
Hu01G06-100	SEQ ID NO: 27	SEQ ID NO: 41
Hu01G06-101	SEQ ID NO: 27	SEQ ID NO: 42
Hu01G06-102	SEQ ID NO: 27	SEQ ID NO: 43
Hu01G06-103	SEQ ID NO: 27	SEQ ID NO: 44
Hu01G06-104	SEQ ID NO: 27	SEQ ID NO: 45
Hu01G06-105	SEQ ID NO: 28	SEQ ID NO: 41
Hu01G06-106	SEQ ID NO: 28	SEQ ID NO: 42
Hu01G06-107	SEQ ID NO: 28	SEQ ID NO: 43
Hu01G06-108	SEQ ID NO: 28	SEQ ID NO: 44
Hu01G06-109	SEQ ID NO: 28	SEQ ID NO: 45
Hu01G06-110	SEQ ID NO: 29	SEQ ID NO: 41
Hu01G06-111	SEQ ID NO: 29	SEQ ID NO: 42
Hu01G06-112	SEQ ID NO: 29	SEQ ID NO: 43
Hu01G06-113	SEQ ID NO: 29	SEQ ID NO: 44
Hu01G06-114	SEQ ID NO: 29	SEQ ID NO: 45
Hu01G06-122	SEQ ID NO: 29	SEQ ID NO: 46
Hu01G06-127	SEQ ID NO: 30	SEQ ID NO: 47
Hu01G06-135	SEQ ID NO: 29	SEQ ID NO: 48
Hu01G06-138	SEQ ID NO: 29	SEQ ID NO: 49
Hu01G06-146	SEQ ID NO: 30	SEQ ID NO: 49
06C11 (murine)	SEQ ID NO: 31	SEQ ID NO: 50
Hu06C11-1	SEQ ID NO: 32	SEQ ID NO: 38
Hu06C11-27	SEQ ID NO: 33	SEQ ID NO: 51
Hu06C11-30	SEQ ID NO: 33	SEQ ID NO: 52
14F11 (murine)	SEQ ID NO: 34	SEQ ID NO: 53
Hu14F11-1	SEQ ID NO: 35	SEQ ID NO: 54
Hu14F11-23	SEQ ID NO: 35	SEQ ID NO: 55
Hu14F11-24	SEQ ID NO: 32	SEQ ID NO: 54
Hu14F11-39	SEQ ID NO: 36	SEQ ID NO: 56
Hu14F11-47	SEQ ID NO: 36	SEQ ID NO: 57

[0023] It is understood that the antibodies described herein can be designed, tested, and formulated using techniques known in the art.

SEQ ID NO: 25

```
  1  diqmtqspas lsasvgetvt itcrtsenlh nylawyqqkq gkspqllvyd aktladgvps

 61  rfsgsgsgtq yslkinslqp edfgsyycqh fwsspytfgg gtkleikrad aaptvsifpp

121  sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt

181  ltkdeyerhn sytceathkt stspivksfn rnec
```

SEQ ID NO: 26

```
  1  diqmtqspas lsasvgetvt itcrtsenlh nylawyqqkq gkspqllvyd aktladgvps

 61  rfsgsgsgtq yslkinslqp edfgsyycqh fwsspytfgg gtkleikrtv aapsvfifpp

121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 27

```
  1  diqmtqspss lsasvgdrvt itcrtsenlh nylawyqqkp gkspkllvyd aktladgvps

 61  rfsgsgsgtd ytltisslqp edfatyycqh fwsspytfgq gtkleikrtv aapsvfifpp

121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 29

```
  1  diqmtqspss lsasvgdrvt itcrtsenlh nylawyqqkp gkapklliyd aktladgvps

 61  rfsgsgsgtd ytltisslqp edfatyycqh fwsspytfgq gtkleikrtv aapsvfifpp

121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 28

```
  1  diqmtqspss lsasvgdrvt itcrtsenlh nylawyqqkp gkspkillyd aktladgvps

 61  rfsgsgsgtd ytltisslqp edfatyycqh fwsspytfgq gtkleikrtv aapsvfifpp

121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 32

```
  1  divmtqsqkf mstsvgdrvs vtckasqnvg tnvawfqqkp gqspkallys asyrysgvpd

 61  rftgsgsgtd filtisnvqs edlaeyfcqq ynnypltfga gtklelkrtv aapsvfifpp

121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 33

```
  1  diqmtqspss lsasvgdrvt itckasqnvg tnvawfqqkp gkapksllys asyrysgvps

 61  rfsgsgsgtd ftltisslqp edfatyycqq ynnypltfgq gtkleikrtv aapsvfifpp

121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 35

```
  1  divmtqsqkf mstsvgdrvs vtckasqnvg tnvawyqqkp gqspkallys psyrysgvpd

 61  rftgsgsgtd ftltisnvqs edlaeyfcqq ynsyphtfgg gtklemkrtv aapsvfifpp

121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 36

```
  1  diqmtqspss lsasvgdrvt itckasqnvg tnvawfqqkp gkspkallys psyrysgvps

 61  rfsgsgsgtd ftltisslqp edfatyfcqq ynsyphtfgq gtkleikrtv aapsvfifpp
```

-continued

```
121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 37

```
  1  evllqqsgpe lvkpgasvki pckasgytft dynmdwvkqs hgkslewigq inpnnggiff

 61  nqkfkgkatl tvdkssntaf mevrsltsed tavyycarea ittvgamdyw gqgtsvtvss

121  akttppsvyp lapgsaaqtn smvtlgclvk gyfpepvtvt wnsgslssgv htfpavlqsd

181  lytlsssvtv psstwpsetv tcnvahpass tkvdkkivpr dcgckpcict vpevssvfif

241  ppkpkdvlti tltpkvtcvv vdiskddpev qfswfvddve vhtaqtqpre eqfnstfrsv

301  selpimhqdw lngkefkcry nsaafpapie ktisktkgrp kapqvytipp pkeqmakdkv

361  sltcmitdff peditvewqw ngqpaenykn tqpimdtdgs yfvysklnvq ksnweagntf

421  tcsvlheglh nhhtekslsh spgk
```

SEQ ID NO: 30

```
  1  diqmtqspss lsasvgdrvt itcrtsenlh nylawyqqkp gkspkillyd aktladgvps

 61  rfsgsgsgtd ytltisslqp edfatyycqh fwsdpytfgq gtkleikrtv aapsvfifpp

121  sdeqlksgta svvcllnnfy preakvqwkv dnalqsgnsq esvteqdskd styslsstlt

181  lskadyekhk vyacevthqg lsspvtksfn rgec
```

SEQ ID NO: 38

```
  1  evllqqsgpe lvkpgasvki pckasgytft dynmdwvkqs hgkslewigq inpnnggiff

 61  nqkfkgkatl tvdkssntaf mevrsltsed tavyycarea ittvgamdyw gqgtsvtvss

121  astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361  mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421  qqgnvfscsv mhealhnhyt qkslslspgk
```

SEQ ID NO: 39

```
  1  qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgkslewigq inpnnggiff

 61  nqkfkgratl tvdtstntay melrslrsdd tavyycarea ittvgamdyw gqgtivtvss

121  astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361  mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421  qqgnvfscsv mhealhnhyt qkslslspgk
```

SEQ ID NO: 40

```
  1  qvqlvqsgae vkkpgssvkv sckasgytft dynmdwvrqa pgkslewigq inpnnggiff

 61  nqkfkgratl tvdkstntay melsslrsed tavyycarea ittvgamdyw gqgtivtvss

121  astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree
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361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421 qqgnvfscsv mhealhnhyt qkslslspgk

SEQ ID NO: 41

1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqglewmgq inpnnggiff

61 nqkfkgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtivtvss

121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421 qqgnvfscsv mhealhnhyt qkslslspgk

SEQ ID NO: 43

1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqslewmgq inpnnggiff

61 nqkfqgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtivtvss

121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421 qqgnvfscsv mhealhnhyt qkslslspgk

SEQ ID NO: 42

1 qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqglewmgq inpnnggiff

61 nqkfqgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtivtvss

121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421 qqgnvfscsv mhealhnhyt qkslslspgk

SEQ ID NO: 44

1 qvqlvqsgae vkkpgssvkv sckasgytfs dynmdwvrqa pgqglewmgq inpnnggiff

61 nqkfkgrvtl tadkststay melsslrsed tavyycarea ittvgamdyw gqgtivtvss

121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181 glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241 psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301 styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361 mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421 qqgnvfscsv mhealhnhyt qkslslspgk

SEQ ID NO: 45

1 qvqlvqsgae vkkpgssvkv sckasgytfs dynmdwvrqa pgqglewmgq inpnnggiff

61 nqkfqgrvtl tadkststay melsslrsed tavyycarea ittvgamdyw gqgtivtvss

121 astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

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181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361  mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421  qqgnvfscsv mhealhnhyt qkslslspgk
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SEQ ID NO: 46

```
  1  qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqslewmgq inpynhliff

 61  nqkfqgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtivtvss

121  astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361  mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421  qqgnvfscsv mhealhnhyt qkslslspgk
```

SEQ ID NO: 47

```
  1  qvqlvqsgae vkkpgasvkv sckasgytft dynmdwvrqa pgqslewmgq inpnngliff

 61  nqkfqgrvtl ttdtststay melrslrsdd tavyycarea ittvgamdyw gqgtivtvss

121  astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361  mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421  qqgnvfscsv mhealhnhyt qkslslspgk
```

SEQ ID NO: 48

```
  1  qvqlvqsgae vkkpgssvkv sckasgytfs dynmdwvrqa pgqglewmgq inpnngliff

 61  nqkfkgrvtl tadkststay melsslrsed tavyycarea ittvgamdyw gqgtivtvss

121  astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361  mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421  qqgnvfscsv mhealhnhyt qkslslspgk
```

SEQ ID NO: 49

```
  1  qvqlvqsgae vkkpgssvkv sckasgytfs dynmdwvrqa pgqglewmgq inpynhliff

 61  nqkfkgrvtl tadkststay melsslrsed tavyycarea ittvgamdyw gqgtivtvss

121  astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361  mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421  qqgnvfscsv mhealhnhyt qkslslspgk
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SEQ ID NO: 38

```
  1  evllqqsgpe lvkpgasvki pckasgytft dynmdwvkqs hgkslewigq inpnnggiff

 61  nqkfkgkatl tvdkssntaf mevrsltsed tavyycarea ittvgamdyw gqgtsvtvss

121  astkgpsvfp lapsskstsg gtaalgclvk dyfpepvtvs wnsgaltsgv htfpavlqss

181  glyslssvvt vpssslgtqt yicnvnhkps ntkvdkrvep kscdkthtcp pcpapellgg

241  psvflfppkp kdtlmisrtp evtcvvvdvs hedpevkfnw yvdgvevhna ktkpreeqyn

301  styrvvsvlt vlhqdwlngk eykckvsnka lpapiektis kakgqprepq vytlppsree

361  mtknqvsltc lvkgfypsdi avewesngqp ennykttppv ldsdgsffly skltvdksrw

421  qqgnvfscsv mhealhnhyt qkslslspgk
```

SEQ ID NO: 51

```
  1  qvtlkesgpa lvkptqtltl tctfsgfsln tygmgvswir qppgkalewl ahiywdddkr

 61  ynpslktrlt iskdtsknqv vltitnvdpv dtavyycaqr gyddywgywg qgtivtissa

121  stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg

181  lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp

241  svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns

301  tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem

361  tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq

421  qgnvfscsvm healhnhytq kslslspgk
```

SEQ ID NO: 52

```
  1  qvtlkesgpt lvkptqtltl tctfsgfsln tygmgvswir qppgkglewl ahiywdddkr

 61  ynpslksrlt itkdtsknqv vltitnmdpv dtatyycaqr gyddywgywg qgtivtvssa

121  stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg

181  lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp

241  svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns

301  tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem

361  tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq

421  qgnvfscsvm healhnhytq kslslspgk
```

SEQ ID NO: 54

```
  1  qvtlkesgpg ilqpsqtlsl tcsfsgfsls tygmgvgwir qpsgkglewl adiwwdddky

 61  ynpslksrlt iskdtssnev flkiaivdta dtatyycarr ghysamdywg qgtsvtvssa

121  stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg

181  lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp

241  svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns

301  tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem

361  tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq

421  qgnvfscsvm healhnhytq kslslspgk
```

SEQ ID NO: 55

```
  1  qvtlkesgpg ilqpsqtlsl tcsfsgfsln tygmgvswir qpsgkglewl ahiywdddkr

 61  ynpslksrlt iskdasnnry flkitsvdta dtatyycaqr gyddywgywg qgtivtisaa

121  stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg

181  lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp
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241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns

301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem

361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq

421 qgnvfscsvm healhnhytq kslslspgk

SEQ ID NO: 56

1 qitlkesgpt lvkptqtltl tctfsgfsls tygmgvgwir qppgkalewl adiwwdddky

61 ynpslksrlt itkdtsknqv vltmtnmdpv dtatyycarr ghysamdywg qgtivtvssa

121 stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg

181 lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp

241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns

301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem

361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq

421 nvfscsvm healhnhytq kslslspgk

SEQ ID NO: 57

1 qvtlkesgpa lvkptqtltl tctfsgfsls tygmgvgwir qppgkalewl adiwwdddky

61 ynpslksrlt iskdtsknqv vltmtnmdpv dtavyycarr ghysamdywg qgtivtvssa

121 stkgpsvfpl apsskstsgg taalgclvkd yfpepvtvsw nsgaltsgvh tfpavlqssg

181 lyslssvvtv pssslgtqty icnvnhkpsn tkvdkrvepk scdkthtcpp cpapellggp

241 svflfppkpk dtlmisrtpe vtcvvvdvsh edpevkfnwy vdgvevhnak tkpreeqyns

301 tyrvvsvltv lhqdwlngke ykckvsnkal papiektisk akgqprepqv ytlppsreem

361 tknqvsltcl vkgfypsdia vewesngqpe nnykttppvl dsdgsfflys kltvdksrwq

421 qgnvfscsvm healhnhytq kslslspgk

SEQ ID NO: 50

1 qvtlkesgpg ilqpsqtlsl tcsfsgfsln tygmgvswir qpsgkglewl ahiywdddkr

61 ynpslksrlt iskdasnnry flkitsvdta dtatyycaqr gyddywgywg qgtivtisaa

121 kttppsvypl apgsaaqtns mvtlgclvkg yfpepvtvtw nsgslssgvh tfpavlqsdl

181 ytlsssvtvp sstwpsetvt cnvahpasst kvdkkivprd cgckpcictv pevssvfifp

241 pkpkdvltit ltpkvtcvvv diskddpevq fswfvddvev htaqtqpree qfnstfrsys

301 elpimhqdwl ngkefkcrvn saafpapiek tisktkgrpk apqvytippp keqmakdkvs

361 ltcmitdffp editvewqwn gqpaenyknt qpimdtdgsy fvysklnvqk snweagntft

421 csvlheglhn hhtekslshs pgk

SEQ ID NO: 31

1 divmtqsqkf mstsvgdrvs vtckasqnvg tnvawfqqkp gqspkaliys asyrysgvpd

61 rftgsgsgtd filtisnvqs edlaeyfcqq ynnypltfga gtklelkrad aaptvsifpp

121 sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt

181 ltkdeyerhn sytceathkt stspivksfn rnec

SEQ ID NO: 53

1 qvtlkesgpg ilqpsqtlsl tcsfsgfsls tygmgvgwir qpsgkglewl adiwwdddky

61 ynpslksrlt iskdtssnev flkiaivdta dtatyycarr ghysamdywg qgtsvtvssa

121 kttppsvypl apgsaaqtns mvtlgclvkg yfpepvtvtw nsgslssgvh tfpavlqsdl

181 ytlsssvtvp sstwpsetvt cnvahpasst kvdkkivprd cgckpcictv pevssvfifp

241 pkpkdvltit ltpkvtcvvv diskddpevq fswfvddvev htaqtqpree qfnstfrsys

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301  elpimhqdwl ngkefkcrvn saafpapiek tisktkgrpk apqvytippp keqmakdkvs

361  ltcmitdffp editvewqwn gqpaenyknt qpimdtdgsy fvysklnvqk snweagntft

421  csvlheglhn hhtekslshs pgk
```

SEQ ID NO: 34

```
  1  divmtqsqkf mstsvgdrvs vtckasqnvg tnvawyqqkp gqspkaliys psyrysgvpd

 61  rftgsgsgtd ftltisnvqs edlaeyfcqq ynsyphtfgg gtklemkrad aaptvsifpp

121  sseqltsgga svvcflnnfy pkdinvkwki dgserqngvl nswtdqdskd stysmsstlt

181  ltkdeyerhn sytceathkt stspivksfn rnec
```

[0024] The antibody may be a neutralizing antibody, which reduces GDF15 activity. For example, the antibody may reduce GDF15 activity in an in vivo assay (see, e.g., Johnen et al., 2007, Nature Medicine 13:1333-1340) by at least 10%, preferably 20%, 30% or 40%, and more preferably at least about 50%, 60%, 80% or 90% of GDF15 compared to GDF15 activity measured in the same assay under the same conditions in the absence of the antibody. The antibody may selectively and/or significantly reduce or inhibit the binding of GDF15 to its endogenous receptor. As used herein, the term "significantly reduces or inhibits binding" of GDF15 to its receptor is understood to mean that the antibody inhibits GDF15 binding with a potency or percent inhibition that measures at least 10%, preferably 20%, 30% or 40%, and more preferably at least about 50%, 60%, 80% or 90% of GDF15 [serum level/activity] in the absence of said antibody. Binding can be measured using a direct or sandwich enzyme-linked immunosorbent assay (ELISA), as described, e.g., in Tsai et al., 2013, PLOS One, 8:e55174. As used herein, the term "selectively" in the context of an antibody that binds to GDF15 or GDF15 receptor is understood to mean that the antibody binds GDF15 or a GDF15 receptor with a binding affinity that is at least two, three, four, five or ten times greater than that of a functionally unrelated protein or another member of the TGF-β superfamily or a receptor of a member of the TGF-β superfamily.

[0025] Methods for reducing or eliminating the antigenicity of antibodies and antibody fragments are known in the art. When the antibodies are to be administered to a human, the antibodies preferably are "humanized" to reduce or eliminate antigenicity in humans. Preferably, each humanized antibody has the same or substantially the same affinity for the antigen as the non-humanized mouse antibody from which it was derived.

[0026] In one humanization approach, chimeric proteins are created in which mouse immunoglobulin constant regions are replaced with human immunoglobulin constant regions. See, e.g., Morrison et al., 1984, Proc. Nat. Acad. Sci. 81:6851-6855, Neuberger et al., 1984, Nature 312:604-608; U.S. Pat. No. 6,893,625 (Robinson); U.S. Pat. No. 5,500,362 (Robinson); and U.S. Pat. No. 4,816,567 (Cabilly).

[0027] In an approach known as CDR grafting, the CDRs of the light and heavy chain variable regions are grafted into frameworks from another species. For example, murine CDRs can be grafted into human FRs. In some embodiments, the CDRs of the light and heavy chain variable regions of an anti-GDF15 antibody are grafted into human FRs or consensus human FRs. To create consensus human FRs, FRs from several human heavy chain or light chain amino acid sequences are aligned to identify a consensus amino acid sequence. CDR grafting is described in U.S. Pat. No. 7,022,500 (Queen); U.S. Pat. No. 6,982,321 (Winter); U.S. Pat. No. 6,180,370 (Queen); U.S. Pat. No. 6,054,297 (Carter); U.S. Pat. No. 5,693,762 (Queen); U.S. Pat. No. 5,859,205 (Adair); U.S. Pat. No. 5,693,761 (Queen); U.S. Pat. No. 5,565,332 (Hoogenboom); U.S. Pat. No. 5,585,089 (Queen); U.S. Pat. No. 5,530,101 (Queen); Jones et al., 1986, Nature 321: 522-525; Riechmann et al., 1988, Nature 332: 323-327; Verhoeyen et al., 1988, Science 239: 1534-1536; and Winter, 1998, FEBS Lett 430: 92-94.

[0028] In an approach called "SUPERHUMANIZATION™," human CDR sequences are chosen from human germline genes, based on the structural similarity of the human CDRs to those of the mouse antibody to be humanized. See, e.g., U.S. Pat. No. 6,881,557 (Foote); and Tan et al., 2002, J. Immunol. 169:1119-1125.

[0029] Other methods to reduce immunogenicity include "reshaping," "hyperchimerization," and "veneering/resurfacing." See, e.g., Vaswami et al., 1998, Annals of Allergy, Asthma, & Immunol. 81:105; Roguska et al., 1996, Prot. Engineer 9:895-904; and U.S. Pat. No. 6,072,035 (Hardman). In the veneering/resurfacing approach, the surface accessible amino acid residues in the murine antibody are replaced by amino acid residues more frequently found at the same positions in a human antibody. This type of antibody resurfacing is described, e.g., in U.S. Pat. No. 5,639,641 (Pedersen).

[0030] Another approach for converting a mouse antibody into a form suitable for medical use in humans is known as ACTIVMAB™ technology (Vaccinex, Inc., Rochester, N.Y.), which involves a vaccinia virus-based vector to express antibodies in mammalian cells. High levels of combinatorial diversity of IgG heavy and light chains are said to be produced. See, e.g., U.S. Pat. No. 6,706,477 (Zauderer); U.S. Pat. No. 6,800,442 (Zauderer); and U.S. Pat. No. 6,872,518 (Zauderer).

[0031] Another approach for converting a mouse antibody into a form suitable for use in humans is technology practiced commercially by KaloBios Pharmaceuticals, Inc. (Palo Alto, Calif.). This technology involves the use of a proprietary human "acceptor" library to produce an "epitope focused" library for antibody selection.

[0032] Another approach for modifying a mouse antibody into a form suitable for medical use in humans is HUMAN ENGINEERING™ technology, which is practiced commercially by XOMA (US) LLC. See, e.g., PCT Publication No. WO 93/11794 and U.S. Pat. No. 5,766,886 (Studnicka); U.S.

Pat. No. 5,770,196 (Studnicka); U.S. Pat. No. 5,821,123 (Studnicka); and U.S. Pat. No. 5,869,619 (Studnicka).

[0033] Any suitable approach, including any of the above approaches, can be used to reduce or eliminate human immunogenicity of an antibody.

[0034] In addition, it is possible to create fully human antibodies in mice. Fully human mAbs lacking any non-human sequences can be prepared from human immunoglobulin transgenic mice by techniques referenced in, e.g., Lonberg et al., Nature 368:856-859, 1994; Fishwild et al., Nature Biotechnology 14:845-851, 1996; and Mendez et al., Nature Genetics 15:146-156, 1997. Fully human mAbs can also be prepared and optimized from phage display libraries by techniques referenced in, e.g., Knappik et al., J. Mol. Biol. 296:57-86, 2000; and Krebs et al., J. Immunol. Meth. 254:67-84 2001).

[0035] It is contemplated that variants and derivatives of GDF15 that act as decoys can be useful in the practice of the invention. For example, through deletion analysis, it may be possible to identify smaller biologically active fragments of GDF15 that compete with endogenous GDF15 for its cognate receptor. Similarly, it is possible to create soluble biologically active fragments of the GDF15 receptor that compete with endogenous GDF15 receptor for available GDF. For example, "biologically active fragments" include, but are not limited to, fragments of a naturally-occurring GDF15 (or homolog) or a GDF15 receptor (or homolog) that compete with endogenous GDF15 or an endogenous GDF15 receptor, respectively, for binding to a cognate binding partner (e.g., GDF15 receptor or GDF15, respectively).

[0036] It is contemplated that antisense nucleic acids (DNA and RNA) and small interfering nucleic acids (e.g., siRNAs) can be designed and used using techniques known in the art. Exemplary siRNA inhibitors of GDF15 include siRNAs from Santa Cruz Biotech (Catalog No. sc-39799, targeting mouse GDF15; and Catalog No. sc-39798, targeting human GDF15), siRNAs from Life Technologies (Cat. Nos. AM16708, 4392420, and 1299001, targeting human GDF15; and Cat. Nos. 1320001 and 4390771, targeting mouse GDF15; and Cat. Nos. 1330001 and 4390771, targeting rat GDF15), siRNAs from Fisher Scientific (Catalog No. NC0683807, targeting human GDF15), siRNAs from Origene (Catalog No. SR306321, targeting human GDF15), siRNAs from amsbio (Catalog No. SR509800, targeting rate GDF15), siRNAs from Dharmacon (including Catalog No. D-019875-02, targeting human GDF15), siRNAs from Sigma-Aldrich (Catalog No. EHU052901, targeting human GDF15), and siRNAs described in Kim et al., 2005, Molecular Cancer Therapeutics, 4:487-493, Chang et al., 2007, Mol. Cancer Therapeutics, 6:2271-2279, and Boyle et al., 2009, J. Invest. Dermatol., 129:383-391.

II. Formulation and Delivery of GDF15 Modulators

[0037] Pharmaceutical compositions containing GDF15 modulators, such as those disclosed herein, can be formulated into dosage forms or dosage units using standard formulation techniques. However, the pharmaceutical composition should be formulated to be compatible with its intended route of administration.

[0038] The compositions described herein can be administered to a subject via any route, including, but not limited to, intravenous (e.g., by infusion pumps), intraperitoneal, intraocular, intra-arterial, intrapulmonary, oral, inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, intraocular, intrathecal, transdermal, transpleural, intraarterial, topical, inhalational (e.g., as mists of sprays), mucosal (such as via nasal mucosa), subcutaneous, transdermal, gastrointestinal, intraarticular, intracistemal, intraventricular, rectal (i.e., via suppository), vaginal (i.e., via pessary), intracranial, intraurethral, intrahepatic, and intratumoral. In some embodiments, the compositions are administered systemically (for example by intravenous injection). In some embodiments, the compositions are administered locally (for example by intraarterial or intraocular injection). A preferred route of administration for GDF15 modulators, such as an antibody, is via intravenous infusion.

[0039] Useful formulations can be prepared by methods well known in the pharmaceutical art. For example, see Remington's Pharmaceutical Sciences, 18th ed. (Mack Publishing Company, 1990). Formulation components suitable for parenteral administration include a sterile diluent such as bacteriostatic water for injection, physiological saline, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. The carrier should be stable under the conditions of manufacture and storage, and should be preserved against microorganisms. In some embodiments, an antibody is lyophilized, and then reconstituted in buffered saline, at the time of administration.

[0040] For therapeutic use, an antibody preferably is combined with a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" means buffers, carriers, and excipients suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers include buffers, solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is known in the art.

[0041] The pharmaceutical compositions preferably are sterile. Sterilization can be accomplished, for example, by filtration through sterile filtration membranes. Where the composition is lyophilized, filter sterilization can be conducted prior to or following lyophilization and reconstitution.

[0042] Generally, a therapeutically effective amount of active component is in the range of 0.1 mg/kg to 100 mg/kg, e.g., 1 mg/kg to 100 mg/kg, 1 mg/kg to 10 mg/kg. The amount administered will depend on variables such as the type and extent of disease or indication to be treated, the overall health of the patient, the in vivo potency of the antibody, the pharmaceutical formulation, and the route of administration. The initial dosage can be increased beyond the upper level in order to rapidly achieve the desired blood-level or tissue-level. Alternatively, the initial dosage can be smaller than the optimum, and the daily dosage may be progressively increased during the course of treatment. Human dosage can be optimized, e.g., in a conventional Phase I dose escalation study designed to run from 0.5

mg/kg to 20 mg/kg. Dosing frequency can vary, depending on factors such as route of administration, dosage amount, serum half-life of the antibody, and the disease being treated. Exemplary dosing frequencies are once per day, once per week and once every two weeks.

[0043] The optimal effective amount of the compositions can be determined empirically and will depend on the type and severity of the disease, route of administration, disease progression and health, mass and body area of the subject. Such determinations are within the skill of one in the art. Examples of dosages of GDF15 modulator molecules which can be used for methods described herein include, but are not limited to, an effective amount within the dosage range of any of about 0.01 μg/kg to about 300 mg/kg, or within about 0.1 μg/kg to about 40 mg/kg, or with about 1 μg/kg to about 20 mg/kg, or within about 1 μg/kg to about 10 mg/kg. For example, when administered subcutaneously, the composition may be administered at low microgram ranges, including for example about 0.1 μg/kg or less, about 0.05 μg/kg or less, or 0.01 μg/kg or less.

[0044] In certain embodiments, the amount of GDF15 modulators administered to a subject is about 10 μg to about 500 mg per dose, including for example any of about 10 μg to about 50 mg, about 50 μg to about 100 mg, about 100 μg to about 200 mg, about 200 μg to about 300 mg, about 300 μg to about 500 mg, about 500 μg to about 1 mg, about 1 mg to about 10 mg, about 10 mg to about 50 mg, about 50 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, about 300 mg to about 400 mg, or about 400 mg to about 500 mg per dose. In certain embodiments, a GDF15 modulator is administered at a dose from about 0.025 mg to about 4 mg, from about 0.035 mg to about 2 mg, from about 0.05 mg to about 2 mg, from about 0.1 mg to about 2 mg, from about 0.2 mg to about 1 mg, or from about 0.2 mg to about 0.8 mg of the GDF15 modulator can be administered. In one embodiment, 0.5 mg of GDF15 modulator is administered locally. In certain other embodiments, from about 0.05 mg to about 2 mg, from about 0.2 mg to about 2 mg, from about 0.05 mg to about 1.5 mg, from about 0.15 mg to about 1.5 mg, from about 0.4 mg to about 1 mg, or from about 0.5 mg to about 0.8 mg of GDF15 modulator is administered locally.

[0045] The GDF15 modulator compositions may be administered in a single daily dose, or the total daily dose may be administered in divided dosages of two, three, or four times daily. The compositions can also be administered less frequently than daily, for example, six times a week, five times a week, four times a week, three times a week, twice a week, once a week, once every two weeks, once every three weeks, once a month, once every two months, once every three months, or once every six months. The compositions may also be administered in a sustained release formulation, such as in an implant which gradually releases the composition for use over a period of time, and which allows for the composition to be administered less frequently, such as once a month, once every 2-6 months, once every year, or even a single administration. The sustained release devices (such as pellets, nanoparticles, microparticles, nanospheres, microspheres, and the like) may be administered by injection or surgical implanted in various locations in the body.

[0046] In certain embodiments of the invention, the dosing of the GDF15 modulator is titrated such that the dose is sufficient to reduce or prevent adverse effects, but yet fully or partially inhibit the activity of the GDF15.

[0047] In some aspects, the activity of GDF15 can be modulated in a target cell using antisense nucleic acids or small interfering nucleic acids. Modulation can be achieved using expression constructs known in the art, e.g., naked DNA constructs, DNA vector based constructs, and/or viral vector and/or viral based constructs to express nucleic acids encoding an anti-GDF15 siRNA or antisense molecule.

[0048] Exemplary DNA constructs and the therapeutic use of such constructs are well known to those of skill in the art (see, e.g., Chiarella et al., 2008, Recent Patents Anti-Infect. Drug Disc., 3:93-101; Gray et al., 2008, Expert Opin. Biol. Ther., 8:911-922; Melman et al., 2008, Hum. Gene Ther., 17:1165-1176). Naked DNA constructs typically include one or more therapeutic nucleic acids (e.g., GDF15 modulators) and a promoter sequence. A naked DNA construct can be a DNA vector, commonly referred to as pDNA. Naked DNA typically do not integrate into chromosomal DNA. Generally, naked DNA constructs do not require, or are not used in conjunction with, the presence of lipids, polymers, or viral proteins. Such constructs may also include one or more of the non-therapeutic components described herein.

[0049] DNA vectors are known in the art and typically are circular double stranded DNA molecules. DNA vectors usually range in size from three to five kilo-base pairs (e.g., including inserted therapeutic nucleic acids). Like naked DNA, DNA vectors can be used to deliver and express one or more therapeutic proteins in target cells. DNA vectors do not integrate into chromosomal DNA.

[0050] Generally, DNA vectors include at least one promoter sequence that allows for replication in a target cell. Uptake of a DNA vector may be facilitated by combining the DNA vector with, for example, a cationic lipid, and forming a DNA complex. Typically, viral vectors are double stranded circular DNA molecules that are derived from a virus. Viral vectors typically are larger in size than naked DNA and DNA vector constructs and have a greater capacity for the introduction of foreign (i.e., not virally encoded) genes. Like naked DNA and DNA vectors, viral vectors can be used to deliver and express one or more therapeutic nucleic acids in target cells. Unlike naked DNA and DNA vectors, certain viral vectors stably incorporate themselves into chromosomal DNA. Typically, viral vectors include at least one promoter sequence that allows for replication of one or more vector encoded nucleic acids, e.g., a therapeutic nucleic acid, in a host cell. Viral vectors may optionally include one or more non-therapeutic components described herein. Advantageously, uptake of a viral vector into a target cell does not require additional components, e.g., cationic lipids. Rather, viral vectors transfect or infect cells directly upon contact with a target cell.

[0051] The approaches described herein include the use of retroviral vectors, adenovirus-derived vectors, and/or adeno-associated viral vectors as recombinant gene delivery systems for the transfer of exogenous genes in vivo, particularly into humans. Protocols for producing recombinant retroviruses and for infecting cells in vitro or in vivo with such viruses can be found in Current Protocols in Molecular Biology, Ausubel, F. M. et al. (eds.) Greene Publishing Associates, 1989, Sections 9.10-9.14, and other standard laboratory manuals.

[0052] Viruses that are used as transduction agents of DNA vectors and viral vectors such as adenoviruses, retro-

viruses, and lentiviruses may be used in practicing the present invention. Illustrative retroviruses include, but are not limited to: Moloney murine leukemia virus (M-MuLV), Moloney murine sarcoma virus (MoMSV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), gibbon ape leukemia virus (GaLV), feline leukemia virus (FLV), spumavirus, Friend murine leukemia virus, Murine Stem Cell Virus (MSCV) and Rous Sarcoma Virus (RSV)) and lentivirus. As used herein, the term "lentivirus" refers to a group (or genus) of complex retroviruses. Illustrative lentiviruses include, but are not limited to: HIV (human immunodeficiency virus; including HIV type 1, and HIV type 2); visna-maedi virus (VMV) virus; the caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV).

[0053] In certain embodiments, an adenovirus can be used in accordance with the methods described herein. The genome of an adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 d1324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are known to those skilled in the art. Recombinant adenoviruses can be advantageous in certain circumstances in that they are not capable of infecting nondividing cells and can be used to infect a wide variety of cell types, including epithelial cells. Furthermore, the virus particle is relatively stable and amenable to purification and concentration, and as above, can be modified so as to affect the spectrum of infectivity. Additionally, introduced adenoviral DNA (and foreign DNA contained therein) is not integrated into the genome of a host cell but remains episomal, thereby avoiding potential problems that can occur as a result of insertional mutagenesis in situ where introduced DNA becomes integrated into the host genome (e.g., retroviral DNA). Moreover, the carrying capacity of the adenoviral genome for foreign DNA is large (up to 8 kilobases) relative to other gene delivery vectors.

[0054] Adeno-associated virus is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. It is also one of the few viruses that may integrate its DNA into nondividing cells, and exhibits a high frequency of stable integration.

[0055] In various embodiments, one or more viral vectors that expresses a therapeutic transgene or transgenes encoding a GDF15 modulator is administered by direct injection to a cell, tissue, or organ of a subject, in vivo. In various other embodiments, cells are transduced in vitro or ex vivo with such a vector encapsulated in a virus, and optionally expanded ex vivo. The transduced cells are then administered to the subject. Cells suitable for transduction include, but are not limited to stem cells, progenitor cells, and differentiated cells. In certain embodiments, the transduced cells are embryonic stem cells, bone marrow stem cells, umbilical cord stem cells, placental stem cells, mesenchymal stem cells, neural stem cells, liver stem cells, pancreatic stem cells, cardiac stem cells, kidney stem cells, or hematopoietic stem cells.

[0056] In particular embodiments, host cells transduced with viral vector of the invention that expresses one or more polypeptides, are administered to a subject to treat chemotherapy-induced cachexia. Other methods relating to the use of viral vectors, which may be utilized according to certain embodiments of the present invention, can be found in, e.g., Kay, 1997, CHEST, 111(6 Supp.):138S-142S; Ferry et al., 1998, Hum. Gene Ther., 9:1975-81; Shiratory et al., 1999, Liver, 19:265-74; Oka et al., 2000, Curr. Opin. Lipidol., 11:179-86; Thule et al., 2000, Gene Ther., 7: 1744-52; Yang, 1992, Crit. Rev. Biotechnol., 12:335-56; Alt, 1995, J. Hepatol., 23:746-58; Brody et al., 1994, Ann. N. Y. Acad. Sci., 716:90-101; Strayer, 1999, Expert Opin. Investig. Drugs, 8:2159-2172; Smith-Arica et al., 2001, Curr. Cardiol. Rep., 3:43-49; and Lee et al., 2000, Nature, 408:483-8.

[0057] Certain embodiments of the invention provide conditional expression of a polynucleotide of interest. For example, expression is controlled by subjecting a cell, tissue, organism, etc., to a treatment or condition that causes the polynucleotide to be expressed or that causes an increase or decrease in expression of the polynucleotide encoded by the polynucleotide of interest. Illustrative examples of inducible promoters/systems include, but are not limited to, steroid-inducible promoters such as promoters for genes encoding glucocorticoid or estrogen receptors (inducible by treatment with the corresponding hormone), metallothionine promoter (inducible by treatment with various heavy metals), MX-1 promoter (inducible by interferon), the "Gene-Switch" mifepristone-regulatable system (Sirin et al., 2003, Gene, 323:67), the cumate inducible gene switch (WO 2002/088346), tetracycline-dependent regulatory systems, etc.

[0058] Conditional expression can also be achieved by using a site specific DNA recombinase. According to certain embodiments of the invention the vector comprises at least one (typically two) site(s) for recombination mediated by a site specific recombinase. As used herein, the terms "recombinase" or "site specific recombinase" include excisive or integrative proteins, enzymes, co-factors or associated proteins that are involved in recombination reactions involving one or more recombination sites (e.g., two, three, four, five, seven, ten, twelve, fifteen, twenty, thirty, fifty, etc.), which may be wild-type proteins (see Landy, 1993, Current Opinion in Biotechnology, 3:699-707), or mutants, derivatives (e.g., fusion proteins containing the recombination protein sequences or fragments thereof), fragments, and variants thereof. Illustrative examples of recombinases suitable for use in particular embodiments of the present invention include, but are not limited to: Cre, Int, IHF, Xis, Flp, Fis, Hin, Gin, OC31, Cin, Tn3 resolvase, TndX, XerC, XerD, TnpX, Hjc, Gin, SpCCE1. and ParA.

[0059] The vectors may comprise one or more recombination sites for any of a wide variety of site specific recombinases. It is to be understood that the target site for a site specific recombinase is in addition to any site(s) required for integration of a vector (e.g., a retroviral vector or lentiviral vector).

[0060] In certain embodiments, vectors comprise a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, hygromycin, methotrexate, Zeocin, Blastocidin, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for Bacilli. Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes

simplex virus thymidine kinase (Wigler et al., 1977, CELL, 11:223-232) and adenine phosphoribosyltransferase (Lowy et al., 1990, CELL, 22:817-823) genes which can be employed in tk- or aprt-cells, respectively.

[0061] All the molecular biological techniques required to generate an expression construct described herein are standard techniques that will be appreciated by one of skill in the art.

[0062] In certain embodiments, DNA delivery may occur parenterally, intravenously, intramuscularly, or even intraperitoneally as described, for example, in U.S. Pat. Nos. 5,543,158; 5,641,515; and 5,399,363 (each specifically incorporated herein by reference in its entirety). Solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0063] In certain embodiments, DNA delivery may occur by use of liposomes, nanocapsules, microparticles, microspheres, lipid particles, vesicles, optionally mixing with cell penetrating polypeptides, and the like, for the introduction of the compositions of the present invention into suitable host cells. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, a nanoparticle or the like. The formulation and use of such delivery vehicles can be carried out using known and conventional techniques.

[0064] Exemplary formulations for ex vivo DNA delivery may also include the use of various transfection agents known in the art, such as calcium phosphate, electroporation, heat shock and various liposome formulations (i.e., lipid-mediated transfection). Particular embodiments of the invention may comprise other formulations, such as those that are well known in the pharmaceutical art, and are described, for example, in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 20th Edition. Baltimore, Md.: Lippincott Williams & Wilkins, 2000.

[0065] In certain embodiments, GDF15 activity is inhibited by contacting a body fluid with a composition comprising a GDF15 modulator ex vivo under conditions that permit the GDF15 modulators to reduce or inhibit GDF15 activity. Suitable body fluids include those that can be returned to the individual, such as blood, plasma, or lymph. Affinity adsorption apheresis is described generally in Nilsson et al., 1988, BLOOD, 58(1):38-44; Christie et al., 1993, TRANSFUSION, 33:234-242; Richter et al., 1997, ASAIO J., 43(1):53-59; Suzuki et al., 1994, AUTOIMMUNITY, 19: 105-112; U.S. Pat. No. 5,733,254; Richter et al., 1993, METABOL. CLIN. EXP., 42:888-894; and Wallukat et al., 1996, INT'L J. CARD., 54:1910195.

[0066] Accordingly, the invention includes methods of treating one or more diseases described herein in a subject comprising treating the subject's blood extracoporeally (i.e., outside the body or ex vivo) with a composition comprising a GDF15 modulator under conditions that permit the modulator to reduce or inhibit GDF15 activity in the blood of the subject.

III. Methods

[0067] The prevention and/or reversal of cachexia, such as cancer anorexia-cachexia syndrome, by use of a GDF15 modulator in combination with anti-cancer treatment is particularly useful in cases where the anti-cancer agent itself may induce or contribute to wasting conditions in the subject being treated. Examples of anti-cancer agents whose treatment and effects can benefit from combination with one or more GDF15 modulators are platinum-based therapeutics such as cisplatin, carboplatin and oxaliplatin. Other anti-cancer agents whose treatment and effects can benefit from combination with one or more GDF15 modulators include: capecitabine, doxorubicin, and gemcitabine.

[0068] The methods of the present invention may also be useful for enhanced therapeutic treatment regimens and/or increase of overall survival in subjects treated with other anti-cancer agents, including alkylating agents; antimetabolites; anti-tumor antibiotics; topoisomerase inhibitors; mitotic inhibitors; corticosteroids; targeted therapies; hormone therapy; immunotherapy; and cancer vaccines. Accordingly, the present invention includes the use of GDF15 modulators, such as antibodies to GDF15, in combination with one or more anti-cancer agents, including: abiraterone (e.g., abiraterone acetate); afatinib (e.g., afatinib dimaleate); aflibercept; aldesleukin; alemtuzumab; anastrazole; asparaginase (e.g., arasparginase *Erwinia chrysanthemi*); arsenic (e.g., arsenic trioxide); axitinib; azacitidine; belinostat; bendamustine (e.g., bendamustine hydrochloride); bevacizumab (e.g., Avastin®); bicalutamide; bisulfan; bleomycin; bortezomib; bosutinib; brentuximab (e.g., brentuximab vedotin); cabazitaxel; cabozantinib (e.g., cabozantinib-S-malate); capecitabine; carboplatin; carfilzomib; carmustine; ceritinib; cetuximab; chlorambucil; cisplatin; clofarabine; crizotinib; cyclophosphamide; cytarabine (e.g., liposomal cytarabine); dabrafenib; dacarbazine; dactinomycin; dasatinib; daunorubicin (e.g., daunorubicin hydrochloride); decitabine; degare; denileukin diftitox; dexamethasone; docetaxel; doxorubicin (e.g., Adriamycin®; doxorubicin hydrochloride; doxorubicin hydrochloride liposome); enzalutamide; epirubicin (e.g., epirubicin hydrochloride); anti-ErbB2 antibodies; anti-ErbB3 antibodies; erlotinib (e.g., erlotinib hydrochloride); etoposide (e.g., etoposide phosphate); everolimus; exemestane; anti-FGFR2 antibodies; anti-FGFR3 antibodies; fludarabine (e.g., fludarabine phosphate); fluorouracil; fulvestrant; gefitinib; gemcitabine (e.g., gemcitabine hydrochloride); goserelin (e.g., goserelin acetate); anti-HGF1 antibodies (e.g., ficlatuzumab); ibrutinib; ibritumomab (e.g., ibritumomab tiuxetan); idelalisib; ifosfamide; imatinib (e.g., imatinib mesylate); imiquimod; ipilimumab; irinotecan (e.g., irinotecan hydrochloride); ixabepilone; lapatinib (e.g., lapatinib ditosylate); lenalidomide; letrozole; leucovorin (e.g., leucovorin calcium; folinic acid); leuprolide (e.g., leuprolide acetate); lomustine; mechlorethamine (e.g., mechlorethemine hydrochloride); megestrol (e.g., megestrol acetate); mesna; mercaptopurine; methotrexate; mitomycin (e.g., mitomycin C); nelarabine; nilotinib; nivolumab; anti-notch1 antibodies; anti-notch3 antibodies; obinutuzumab; ofatumumab; omacetaxine (e.g., omacetaxine mepesuccinate); oxaliplatin; paclitaxel (e.g., paclitaxel albumin-stabilized nanoparticle formulation); pamidronate (e.g., pamidronate disodium); panitumumab; pazopanib (e.g., pazopanib hydrochloride); pegaspargase; pemetrexed (e.g., pemetrexed disodium); pertuzumab; plerixafor; pomalidomide; pona-

tinib (e.g., ponatanib hydrochloride); pralatrexate; prednisone; procarbazine (e.g., procarbazine hydrochloride); radium 223 (e.g., radium 223 dichloride); ramucirumab; recombinant HPV vaccines (e.g., Cervarix®, Gardasil®); recombinant interferon (e.g., interferon alfa-2b; pegylated interferon alfa-2b); pembrolizumab; regorafenib; rituximab; romidepsin; ruxolitinib (e.g., ruxolitinib phosphate); siltuximab; sipuleucel-T; sorafenib (e.g., sorafenib tosylate); sunitinib (e.g., sunitinib malate); tamoxifen (e.g., tamoxifen citrate); temozolomide; temsirolimus; thalidomide; tivozanib; topotecan (e.g., topotecan hydrochloride); toremifene; tositumomab (e.g., tositumomab and iodine); trametinib; trastuzumab (e.g., Herceptin®; Kadcyla®); vandetanib; vemurafenib; vinblastine (e.g., vinblastine sulfate); vincristine (e.g., vincristine sulfate); vismodegib; vorinostat; and zoledronic acid.

[0069] In certain embodiments, the GDF15 modulator is used with combinations of one or more of the above cancer treatment agents, including but not limited to, the following combinations of anti-cancer agents: AC [Adriamycin (i.e., doxorubicin hydrochloride)+cyclophosphamide]; ACT [Adriamycin® (i.e., doxorubicin hydrochloride)+cyclophosphamide+Taxol® (i.e. paclitaxel); CAF [cyclophosphamide+Adriamycin® (i.e., doxorubicin hydrochloride)+fluorouracil]; CMF [cyclophosphamide+methotrexate+fluorouracil]; FEC [fluorouracil+epirubicin hydrochloride+cyclophosphamide]; TAC [Taxotere® (i.e. docetaxel)+Adriamycin® (i.e., doxorubicin hydrochloride)+cyclophosphamide]; CAPDX [capecitabine+oxaliplatin]; FOLFIRI [Folinic acid (i.e., leucovorin calcium)+fluorouracil+irinotecan hydrochloride]; FOLFIRI+bevacizumab; FOLFIRI+cetuximab; FOLFOX [Folinic acid (i.e., leucovorin calcium)+fluorouracil+oxaliplatin]; XELOX [Xeloda® (i.e., capecitabine)+oxaliplatin]; Hyper-CVAD [cyclophosphamide+vincristine sulfate+Adriamycin® (i.e., doxorubicin hydrochloride)+dexamethasone]; ADE [Ara-C (i.e., cytarabine)+daunorubicin hydrochloride+etoposide]; chlorambucil+prednisone; CVP [chlorambucil+vincristine sulfate+prednisone]; carboplatin-paclitaxel; carboplatin-taxol; gemcitabine-cisplatin; gemcitabine-oxaliplatin; ABVD [Adriamycin® (i.e., doxorubicin hydrochloride)+bleomycin+vincristine sulfate+dacarbazine]; ABVE [Adriamycin® (i.e., doxorubicin hydrochloride)+bleomycin+vincristine sulfate+etoposide]; ABVE-PC [Adriamycin® (i.e., doxorubicin hydrochloride)+bleomycin+vincristine sulfate+etoposide+prednisone+cyclophosphamide]; BEACOPP [bleomycin+etoposide+Adriamycin® (i.e., doxorubicin hydrochloride)+cyclophosphamide+Oncovin® (i.e., vincristine sulfate+procarbazine hydrochloride+prednisone]; COPP [cyclophosphamide+Oncovin® (i.e., vincristine sulfate+procarbazine hydrochloride+prednisone]; COPP-ABV [cyclophosphamide+Oncovin® (i.e., vincristine sulfate)+procarbazine hydrochloride+prednisone+Adriamycin® (i.e., doxorubicin hydrochloride)+bleomycin+vinblastine sulfate]; ICE [Ifosfamide+carboplatin+etoposide]; MOPP [mechlorethamine hydrochloride+Oncovin® (i.e., vincristine sulfate)+procarbazine hydrochloride+prednisone]; OEPA [Oncovin® (i.e., vincristine sulfate)+etoposide+prednisone+Adriamycin® (i.e., doxorubicin hydrochloride)]; OPPA [Oncovin® (i.e., vincristine sulfate)+procarbazine hydrochloride+prednisone+Adriamycin® (i.e., doxorubicin hydrochloride)]; Stanford V combination [mechloroethamine hydrochloride+doxorubuicin hydrochloride+vinblastine sulfate+vincristine sulfate+bleomycin+etoposide+prednisone]; VAMP [vincristine sulfate+Adriamycin® (i.e., doxorubicin hydrochloride)+methotrexate+prednisone]; CHOP [cyclophosphamide+Hydroxydaunomycin® (i.e., doxorubincin hydrochloride)+Oncovin (i.e., vincristine sulfate)+prednisone]; R-CHOP [rituximab+cyclophosphamide+Hydroxydaunomycin® (i.e., doxorubincin hydrochloride)+Oncovin® (i.e., vincristine sulfate)+prednisone]; EPOCH [etoposide+prednisone+Oncovin® (i.e., vincristine sulfate)+cyclophosphamide+Hydroxydaunomycin® (i.e., doxorubincin hydrochloride)]; PAD [PS-341 (i.e., bortezomib)+Adriamycin® (i.e., doxorubicin hydrochloride)+dexamethasone]; BEP [bleomycin+etoposide+Platinol® (i.e., cisplatin); VeIP [Velban® (i.e., vinblastine sulfate)+ifosfamide+Platinol® (i.e., cisplatin)+mesna]; OFF [oxaliplatin+fluorouracil+Folinic Acid (i.e., leucovorin calcium)].

[0070] Exemplary indications for the methods of the present invention include the following tumors and cancers: breast cancer; lung cancer (including small cell and non-small cell lung cancer); anal, colon, rectal and colorectal cancer; liver cancer; kidney and renal cancer (including renal cell carcinoma); head and neck cancer; pancreatic cancer; bone cancer; cervical, ovarian, vaginal and vulvar cancer; prostate, penile and testicular cancer; anal cancer; bladder cancer; leukemia (including AML; CML; ALL and CLL); stomach cancer (including gastrointestinal stromal tumors) and gastric cancer; brain tumors; gliomas; neuroblastomas and retinoblastomas; thyroid cancer; skin cancer (including melanoma); multiple myeloma (and other plasma cell neoplasms); lymphoma (including Hodgkin's and non-Hodgkin's); sarcoma; myeloproliferative neoplasms; malignant mesothelioma; adult/childhood soft tissue sarcoma; AIDS related Kaposi Sarcoma; endometrial cancer; gestational trophoblastic disease; malignant mesothelioma; multicentric Castleman Disease; myeloproliferative neoplasms; rhabdomyosarcoma; basal cell carcinoma; Wilms tumor and other childhood kidney cancers.

[0071] In certain embodiments, one or more anti-cachexia agents may be used in addition to, or as substitute for, a GDF15 modulator. Anti-cachexia agents that may be useful in the present invention include megestrol acetate (Agiles et al. (2013) Clinical Nutrition 32:319-324); corticosteroids or glucocorticoids (such as dexamethasone, prednisone, methyl prednisolone); cannabinoids (such as dronabinol); ghrelin and anamorelin; melanocortin antagonists; anti-IL6 monoclonal antibodies; selective androgen receptor modulators (SARS); thalidomide; oxandrolone; activin receptor II; GDF8 (myostatin); and IL-la inhibitors.

IV: Preferred Embodiments

[0072] In preferred embodiments of the invention, subjects may be pre-treated with a GDF15 modulator, such as a GDF15 inhibitory antibody, prior to or concomitant with treatment with one or more anti-cancer agents. Dosage and administration of a GDF15 modulator may be determined by the skilled clinician. In some embodiments, the amount of GDF15 modulator administered to an individual is about 10 μg to about 500 mg per dose, including for example any of about 10 μg to about 50 μg, about 50 μg to about 100 μg, about 100 μg to about 200 μg, about 200 μg to about 300 μg, about 300 μg to about 500 μg, about 500 μg to about 1 mg, about 1 mg to about 10 mg, about 10 mg to about 50 mg, about 50 mg to about 100 mg, about 100 mg to about 200 mg, about 200 mg to about 300 mg, about 300 mg to about 400 mg, or about 400 mg to about 500 mg per dose. In

particular preferred embodiments, the GDF15 modulator is a GDF15 antibody selected from the group consisting of Hu01G06-135 and Hu01G06-127. See WO 2014/100689, the disclosure of which is hereby incorporated by reference.

[0073] The GDF15 modulator compositions may be administered in a single daily dose, or the total daily dose may be administered in divided dosages of two, three, or four times daily. The compositions can also be administered less frequently than daily, for example, six times a week, five times a week, four times a week, three times a week, twice a week, once a week, once every two weeks, once every three weeks, once a month, once every two months, once every three months, or once every six months. The compositions may also be administered in a sustained release formulation, such as in an implant which gradually releases the composition for use over a period of time, and which allows for the composition to be administered less frequently, such as once a month, once every 2-6 months, once every year, or even a single administration. The sustained release devices (such as pellets, nanoparticles, microparticles, nanospheres, microspheres, and the like) may be administered by injection or surgical implanted in various locations in the body.

[0074] In certain preferred embodiments of the invention, the subject is treated with capecitabine (for example, Xeloda®) for cancer of the colon or rectum that has spread to other parts of the body (metastatic colorectal cancer), or cancer of the colon after surgery. Prior to, concomitant with, or subsequent to treatment with capecitabine, the subject is treated with anti-GDF15 antibody as a GDF15 modulator.

[0075] In other embodiments, the subject is treated with capecitabine in combination with, or after treatment with, docetaxel (e.g., Taxotere®) for breast cancer that has spread to other parts of the body (metastatic breast cancer). Prior to, concomitant with, or subsequent to treatment with capecitabine, the subject is treated with anti-GDF15 antibody as a GDF15 modulator.

[0076] Dosage and administration of capecitabine may be determined by the skilled clinician. A typical regimen may comprise administration of 1250 mg/ml^2 administered orally twice per day for two weeks, followed by a one week resting period, as a three week cycle. When used in combination with docetaxel, a typical regimen for docetaxel is 75 mg/ml^2 as one hour intravenous infusion every 3 weeks.

[0077] In certain preferred embodiments of the invention, the subject is treated with gemcitabine (for example, Gemzar®), for pancreatic cancer; for ovarian in combination with carboplatin; for breast cancer in combination with paclitaxel; for non-small cell lung cancer (NSCLC) in combination with cisplatin. Prior to, concomitant with, or subsequent to treatment with gemcitabine, the subject is treated with anti-GDF15 antibody as a GDF15 modulator.

[0078] Dosage and administration of gemcitabine may be determined by the skilled clinician. A typical regimen may comprise administration of between 1000 and 1250 mg/ml^2 administered intravenously over 30 minutes on days 1 and 8 of each 21 day cycle; or days 1, 8 and 15 of each 28 day cycle.

[0079] In certain preferred embodiments of the invention, the subject is treated with doxorubicin (for example, Adriamycin®) for cancer of the colon or rectum that has spread to other parts of the body (metastatic colorectal cancer), or cancer of the colon after surgery. Prior to, concomitant with, or subsequent to treatment with capecitabine, the subject is treated with anti-GDF15 antibody as a GDF15 modulator.

[0080] Doxorubicin (for example Doxil®) is also approved for treatment of ovarian cancer, AIDS-related Kaposi's Sarcoma; and multiple myeloma, in combination with bortezomib, as well as for acute lymphoblastic lymphoma (ALL); acute myeloblastic lymphoma (AML); neuroblastoma; breast carcinoma; ovarian carcinoma; Hodgkin's Disease; malignant lymphoma; and bronchogenic carcinoma in which the small cell type is the most responsive compared to other cell types. Prior to, concomitant with, or subsequent to treatment with doxorubicin, the subject is treated with anti-GDF antibody as a GDF modulator.

[0081] Dosage and administration of doxorubicin may be determined by the skilled clinician. A typical regimen may comprise administration of between 50 mg/ml^2 administered intravenously every 4 weeks, for four courses minimum (ovarian cancer); 20 mg/ml^2 administered intravenously every three weeks for treatment of AIDS-related Kaposi's Sarcoma. In multiple myeloma, a typical regimen is administration of bortezomib at 1.3 mg/ml^2, administered as an intravenous bolus injection on days 1, 4, 8 and 11 every 3 weeks, and administration of doxorubicin at 30 mg/ml^2, administered intravenously on day 4 following the administration of bortezomib.

[0082] In certain preferred embodiments of the invention, the subject is treated with carboplatin, for example, Paraplatin®, for ovarian cancer. In other embodiments, the subject is treated with carboplatin in combination with, or after treatment with cyclophosphamide for advanced ovarian cancer. Prior to, concomitant with, or subsequent to treatment with carboplatin, the subject is treated with anti-GDF15 antibody as a GDF15 modulator.

[0083] Dosage and administration of carboplatin may be determined by the skilled clinician. A typical regimen may comprise administration 300-360 mg/ml^2 intravenous on day 1 every 4 weeks for approximately 6 cycles. When cyclophosphamide is co-administered, a typical regimen may be 300 mg/ml^2 intravenous infusion of carboplatin one day every 4 weeks for 6 cycles, combined with 600 mg/ml^2 intravenous infusion of cyclophosphamide one day every 4 weeks for 6 cycles.

[0084] In certain preferred embodiments of the invention, the subject is treated with cisplatin, for example, Platinol®, for the treatment of metastatic testicular tumors, metastatic ovarian tumors, or advanced bladder cancer. In other embodiments, the subject is treated with cisplatin in combination with, or after treatment with cyclophosphamide. Prior to, concomitant with, or subsequent to treatment with cisplatin, the subject is treated with anti-GDF15 antibody as a GDF15 modulator.

[0085] Dosage and administration of cisplatin may be determined by the skilled clinician. A typical regimen may comprise administration 20 mg/ml^2 intravenous daily for 5 days per cycle for metastatic testicular tumors. For advanced bladder cancer, a typical regimen for cisplatin may comprise 50-70 mg/ml^2 intravenous infusion once every 3 to 4 weeks, depending upon the extent of prior exposure to radiation therapy and/or prior chemotherapy. For heavily pretreated patients, a dose of 50 mg/ml^2 intravenous once every 4 weeks is typical. For treatment of metastatic ovarian tumors, 75 to 100 mg/ml^2 intravenous per cycle once every 4 weeks is typical. When cisplatin administration is combined with cyclophosphamide, cisplatin injection and cyclophosph-

amide should be administered sequentially. A typical regimen may be 600 mg/ml^2 intravenous infusion of cyclophosphamide on day 1 every 4 weeks.

[0086] In certain preferred embodiments of the invention, the subject is treated with oxaliplatin, for example Eloxatin®, in combination with 5-fluorouracil and/or leucovorin, for treatment of cancer of the colon or advanced colorectal cancer, or cancer of the colon after surgery. Prior to, concomitant with, or subsequent to treatment with oxaliplatin, the subject is treated with anti-GDF15 antibody as a GDF15 modulator.

[0087] Dosage and administration of oxaliplatin may be determined by the skilled clinician. A typical regimen may comprise administration 85 mg/ml^2 intravenous infusion of oxaliplatin in 250-500 ml 5% dextrose, over 120 minutes, at the same time as 200 mg/ml^2 intravenous infusion of leucovorin, followed by 400 mg/ml^2 of 5-fluorouracil intravenous bolus given over 4-6 minutes.

Examples

[0088] The following Examples are merely illustrative and are not intended to limit the scope or content of the invention in any way.

Example 1: Inhibition of GDF15 in Cancer Cachexia Tumor-Bearing Mice

[0089] This Example demonstrates the increase in overall survival of mice bearing LNCaP prostate xenograft model when treated with a GDF15 modulator in combination with an anti-cancer agent (e.g., tivozanib). LNCaP cells were grown in culture at 37° C. in an atmosphere containing 5% CO_2, using RPMI-1640 Medium (ATCC® 30-2001™) containing 10% FBS. Cells were inoculated subcutaneously into the flank of 8-week old female NCR Nude mice with 5×106 cells per mouse in 50% matrigel. When tumor size reached 500 mm^3, the mice were randomized into three groups of ten mice each. Each group received one of the following treatments: (1) murine immunoglobulin G (20 mpk) and vehicle (Control); (2) murine anti-GDF15 antibody 14F11 (20 mpk) and tivozanib (5 mpk); or (3) murine immunoglobulin G (20 mpk) and tivozanib (5 mpk). Antibodies were administered every 3 days by intra-peritoneal injection, tivozanib and vehicle control was administered daily by oral gavage. Body weight and tumor size were measured daily. Mice were evaluated daily and if any of the following criteria were achieved, animals were sacrificed: a) tumor size larger than 2,000 mm^3; b) body weight loss greater than 20%; c) moribund.

[0090] Treatment with the anti-tumor agent tivozanib, an angiogenesis inhibitor, slows down tumor growth. In the absence of GDF15 inhibition, 70% of the mice die due to cachexia over a period of 30 days, even in the presence of anti-cancer treatment. However, as shown in FIG. **1**, the combination of GDF15 inhibition with anti-cancer agent tivozanib reverses cachexia, and results in 100% sustained survival, and effective anti-tumor treatment over the 30 day period.

Example 2: Inhibition of GDF15 in Cisplatin-Induced Cachexia Model

[0091] This Example demonstrates the increase in overall survival of mice treated with an anti-cancer agent (e.g., cisplatin) when a GDF15 modulator is administered. Naive non-tumor-bearing, 8-week old, female, ICR-Scid mice were treated with cisplatin (3 mpk) twice a week by intraperitoneal injection. Body weight was measured daily. After 2 doses of cisplatin (day 0 of the experiment) mice were randomized into two groups of ten mice each. One group received cisplatin 3 mpk plus (1) vehicle; or cisplatin 3 mpk with (2) rabbit monoclonal antibody raised against murine anti-GDF15 antibody, R-23 twice a week (20 mpk) by intra-peritoneal injection. In the absence of GDF15 inhibition, 80% of the mice die due to cachexia caused by the cisplatin agent over a period of 9 days. However, as shown in FIG. **2**, the combination of GDF15 inhibition with cisplatin treatment resulted in 100% sustained survival over the 9 day period.

Example 3: Inhibition of GDF15 in Carboplatin-Induced Cachexia Model

[0092] This Example demonstrates the increase in overall survival of mice treated with an anti-cancer agent (e.g., carboplatin) when a GDF15 modulator is administered. Naive non-tumor-bearing, 8-week old, female, ICR-Scid mice were treated with carboplatin (60 mpk) by intraperitoneal injection on Day 0 and Day 3 of this experiment. On Day 2, after mice experience 8% body weight loss, mice were randomized into two groups of ten mice each. One group received carboplatin (60 mpk) plus (1) vehicle or carboplatin (60 mpk) plus (2) rabbit monoclonal antibody raised against murine anti-GDF15 antibody, R-23 (20 mpk) by intra-peritoneal injection on Day 2 and Day 4. In the absence of GDF15 inhibition, 80% of the mice died due to cachexia caused by the carboplatin agent over a period of 8 days. However, as shown in FIG. **3**, the combination of GDF15 inhibition with carboplatin treatment resulted in sustained survival over the 8 day period.

Example 4: Inhibition of GDF15 in Oxaliplatin-Induced Cachexia Model

[0093] This Example demonstrates the increase in overall survival of mice treated with an anti-cancer agent (e.g., oxaliplatin) when a GDF15 modulator is administered. Naive non-tumor-bearing, 8-week old, female, ICR-Scid mice were treated daily with oxaliplatin (3 mpk) by intraperitoneal injection. On Day 3, after mice experience 8% body weight loss, mice were randomized into two groups of ten mice each. One group received oxaliplatin (3 mpk) plus (1) vehicle; or oxaliplatin (3 mpk) plus (2) rabbit monoclonal antibody raised against murine anti-GDF15 antibody, R-23 (20 mpk). Antibody or vehicle was dosed on Day 3, 5, 7, 9 by intra-peritoneal injection. In the absence of GDF15 inhibition, 45% of the mice die due to cachexia caused by the oxaliplatin agent over a period of 10 days. However, as shown in FIG. **4**, the combination of GDF15 inhibition with oxaliplatin treatment resulted in sustained survival over the 10 day period.

INCORPORATION BY REFERENCE

[0094] The entire disclosure of each of the patent documents and scientific articles referred to herein, including U.S. Pat. No. 8,192,735; WO 2014/100689 (corresponding to U.S. Patent Publication No. US 2014-0193427-A1); and International Patent Application Nos. PCT/US2015/036790 and PCT/US2015/036794, is incorporated by reference for all purposes.

EQUIVALENTS

[0095] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and the range of equivalency of the claims are intended to be embraced therein.

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Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 29
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"
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<400> SEQUENCE: 29

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Glu Asn Leu His Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Lys Thr Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Phe Trp Ser Ser Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 30
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 30

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Glu Asn Leu His Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Lys Thr Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln His Phe Trp Ser Asp Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

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Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 31
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 31

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20                  25                  30

Val Ala Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
        35                  40                  45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Asn Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175

Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210
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<210> SEQ ID NO 32
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 32

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1 5 10 15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Phe Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr Ile Ser Asn Val Gln Ser
65 70 75 80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Asn Tyr Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 33
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 33

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
20 25 30

Val Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
35 40 45

Tyr Ser Ala Ser Tyr Arg Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly

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    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Asn Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 34
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 34

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
        35                  40                  45

Tyr Ser Pro Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro His
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Met Lys Arg Ala Asp Ala Ala
            100                 105                 110

Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly
        115                 120                 125

Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile
    130                 135                 140

Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu
145                 150                 155                 160

Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser
                165                 170                 175
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Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr
            180                 185                 190

Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser
        195                 200                 205

Phe Asn Arg Asn Glu Cys
    210


<210> SEQ ID NO 35
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 35

Asp Ile Val Met Thr Gln Ser Gln Lys Phe Met Ser Thr Ser Val Gly
1               5                   10                  15

Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Ala Leu Ile
        35                  40                  45

Tyr Ser Pro Ser Tyr Arg Tyr Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Asn Val Gln Ser
65                  70                  75                  80

Glu Asp Leu Ala Glu Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro His
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Leu Glu Met Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 36
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 36
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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20                  25                  30

Val Ala Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Ala Leu Ile
        35                  40                  45

Tyr Ser Pro Ser Tyr Arg Tyr Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Tyr Asn Ser Tyr Pro His
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 37
<211> LENGTH: 444
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 37

Glu Val Leu Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Ile Pro Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Asn Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45

Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asn Thr Ala Phe
65                  70                  75                  80

Met Glu Val Arg Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val
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        115                 120                 125

Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr
    130                 135                 140

Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr
145                 150                 155                 160

Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser
            180                 185                 190

Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala
        195                 200                 205

Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys
    210                 215                 220

Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe
225                 230                 235                 240

Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val
                245                 250                 255

Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe
            260                 265                 270

Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro
        275                 280                 285

Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro
    290                 295                 300

Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val
305                 310                 315                 320

Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr
                325                 330                 335

Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys
            340                 345                 350

Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp
        355                 360                 365

Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro
    370                 375                 380

Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser
385                 390                 395                 400

Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala
                405                 410                 415

Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His
            420                 425                 430

His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440


<210> SEQ ID NO 38
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 38

Glu Val Leu Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1               5                   10                  15
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Ser Val Lys Ile Pro Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Asn Met Asp Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45

Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Asn Thr Ala Phe
65                  70                  75                  80

Met Glu Val Arg Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415
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Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 39
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 39

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45

Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Val Asp Thr Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
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    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 40
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 40

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Lys Ser Leu Glu Trp Ile
        35                  40                  45

Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Ala Thr Leu Thr Val Asp Lys Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175
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Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 41
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 41

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Asn Met Asp Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45
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Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
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450

<210> SEQ ID NO 42
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence: Synthetic polypeptide"

<400> SEQUENCE: 42

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

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

Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

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Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 43
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 43

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

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

Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
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Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 44
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 44

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
            20                  25                  30

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

Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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               85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 45
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 45

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
            20                  25                  30

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

Gly Gln Ile Asn Pro Asn Asn Gly Gly Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365
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```
Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 46
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 46

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

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

Gly Gln Ile Asn Pro Tyr Asn His Leu Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
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               245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 47
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 47

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

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

Gly Gln Ile Asn Pro Asn Asn Gly Leu Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Leu Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125
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```
Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 48
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 48
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```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
            20                  25                  30

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

Gly Gln Ile Asn Pro Asn Asn Gly Leu Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
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               405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
           420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
       435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 49
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 49

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp Tyr
           20                  25                  30

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

Gly Gln Ile Asn Pro Tyr Asn His Leu Ile Phe Phe Asn Gln Lys Phe
    50                  55                  60

Lys Gly Arg Val Thr Leu Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Ala Ile Thr Thr Val Gly Ala Met Asp Tyr Trp Gly Gln
           100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
       115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
           180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
       195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
           260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
       275                 280                 285
```

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```
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 50
<211> LENGTH: 443
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 50

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Asn Thr Tyr
            20                  25                  30

Gly Met Gly Val Ser Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45

Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Ala Ser Asn Asn Arg Val
65                  70                  75                  80

Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Gln Arg Gly Tyr Asp Asp Tyr Trp Gly Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Ile Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr
        115                 120                 125

Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp
145                 150                 155                 160
```

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Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser
            180                 185                 190

Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys
    210                 215                 220

Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro
225                 230                 235                 240

Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr
                245                 250                 255

Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser
            260                 265                 270

Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg
        275                 280                 285

Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile
    290                 295                 300

Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn
305                 310                 315                 320

Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
                325                 330                 335

Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu
            340                 345                 350

Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe
        355                 360                 365

Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala
    370                 375                 380

Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr
385                 390                 395                 400

Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly
                405                 410                 415

Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His
            420                 425                 430

Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440


<210> SEQ ID NO 51
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 51

Gln Val Thr Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Asn Thr Tyr
            20                  25                  30

Gly Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45

Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
```

-continued

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    50                  55                  60

Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Ile Thr Asn Val Asp Pro Val Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Gln Arg Gly Tyr Asp Asp Tyr Trp Gly Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Ile Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
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-continued

<210> SEQ ID NO 52
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 52

Gln Val Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Asn Thr Tyr
20 25 30

Gly Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu
35 40 45

Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Ile Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Gln Arg Gly Tyr Asp Asp Tyr Trp Gly Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr

-continued

```
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
```

<210> SEQ ID NO 53
<211> LENGTH: 443
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 53

```
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Tyr
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Glu Val
65                  70                  75                  80

Phe Leu Lys Ile Ala Ile Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Arg Gly His Tyr Ser Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Ser Val Thr Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr
        115                 120                 125

Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu
    130                 135                 140

Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp
145                 150                 155                 160

Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser
            180                 185                 190

Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser
        195                 200                 205

Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys
    210                 215                 220
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-continued

```
Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro
225                 230                 235                 240

Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr
                245                 250                 255

Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser
            260                 265                 270

Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg
        275                 280                 285

Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile
    290                 295                 300

Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn
305                 310                 315                 320

Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
                325                 330                 335

Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu
            340                 345                 350

Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe
        355                 360                 365

Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala
    370                 375                 380

Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr
385                 390                 395                 400

Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly
                405                 410                 415

Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His
            420                 425                 430

Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
        435                 440


<210> SEQ ID NO 54
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 54

Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Tyr
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Ser Asn Glu Val
65                  70                  75                  80

Phe Leu Lys Ile Ala Ile Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Arg Gly His Tyr Ser Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
```

-continued

```
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
```

<210> SEQ ID NO 55
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 55

-continued

```
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Asn Thr Tyr
            20                  25                  30

Gly Met Gly Val Ser Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45

Trp Leu Ala His Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Ala Ser Asn Asn Arg Val
65                  70                  75                  80

Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Gln Arg Gly Tyr Asp Asp Tyr Trp Gly Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Ile Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
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```
               405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
           420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
       435                 440                 445

Lys


<210> SEQ ID NO 56
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 56

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1               5                   10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Tyr
           20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
       35                  40                  45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Arg Gly His Tyr Ser Ala Met Asp Tyr Trp Gly Gln Gly
           100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
       115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
           180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
       195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
           260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
       275                 280                 285
```

-continued

```
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 57
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 57

Gln Val Thr Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Tyr
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Arg Gly His Tyr Ser Ala Met Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
```

-continued

```
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys
```

What is claimed is:

1. A method for increasing the overall survival in a subject having cancer anorexia-cachexia syndrome, comprising treating the subject with at least one anti-cancer agent and at least one GDF15 modulator.

2. The method of claim **1**, wherein the anti-cancer agent is selected from the group consisting of: capecitabine, gemcitabine, doxorubicin, cisplatin, carboplatin and oxaliplatin.

3. The method of claim **1**, wherein the GDF15 modulator is an anti-GDF15 antibody, or a GDF15-binding fragment thereof.

4. A method for increasing the overall survival in a subject being treated with an anti-cancer agent, comprising further treating the subject with at least one GDF15 modulator.

5. The method of claim **4**, wherein the anti-cancer agent is selected from the group consisting of: capecitabine, gemcitabine, doxorubicin, cisplatin, carboplatin and oxaliplatin.

6. The method of claim **4**, wherein the GDF15 modulator is an anti-GDF15 antibody, or a GDF15-binding fragment thereof.

7. The method of claim **4**, wherein the anti-cancer agent induces cachexia.

8. A method for increasing the overall survival in a subject bearing a cachexia-inducing tumor, comprising treating the subject with at least one anti-cancer agent and at least one GDF15 modulator.

9. The method of claim **8**, wherein the anti-cancer agent is selected from the group consisting of: capecitabine, gemcitabine, doxorubicin, cisplatin, carboplatin and oxaliplatin.

10. The method of claim **8**, wherein the GDF15 modulator is an anti-GDF15 antibody, or a GDF15-binding fragment thereof.

11. A method of treating a subject with cancer anorexia-cachexia syndrome, the method comprising administering a GDF15 modulator and an anti-cancer agent, wherein administration of the GDF15 modulator and the anti-cancer agent

prolongs mean survival in a first patient population with cancer anorexia-cachexia syndrome relative to a second patient population with cancer anorexia-cachexia syndrome who do not receive the GDF15 modulator.

12. The method of claim **11**, wherein the anti-cancer agent is selected from the group consisting of: capecitabine, gemcitabine, doxorubicin, cisplatin, carboplatin and oxaliplatin.

13. The method of claim **11**, wherein the GDF15 modulator is an anti-GDF15 antibody, or a GDF15-binding fragment thereof.

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