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(54) **IL-22 FC FUSION PROTEIN AND METHODS OF USE**

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(63) Continuation of application No. 15/842,493, filed on Dec. 14, 2017, now abandoned, which is a continuation of application No. 15/588,103, filed on May 5, 2017, now abandoned, which is a continuation of application No. 15/276,511, filed on Sep. 26, 2016, now abandoned, which is a continuation of application No. 15/019,845, filed on Feb. 9, 2016, now abandoned, which is a continuation of application No. 14/751,251, filed on Jun. 26, 2015, now abandoned, which is a continuation of application No. 14/535,579, filed on Nov. 7, 2014, now abandoned, which is a continuation of application No. 14/216,802, filed on Mar. 17, 2014, now abandoned.

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A61K 31/573	(2006.01)
A61K 45/06	(2006.01)
A61P 1/04	(2006.01)

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

CPC ***C07K 14/54*** (2013.01); ***C07K 7/06*** (2013.01); ***A61K 38/20*** (2013.01); *C07K 2319/30* (2013.01); ***A61K 45/06*** (2013.01); ***A61P 1/04*** (2018.01); ***A61K 31/573*** (2013.01)

(57) **ABSTRACT**

The invention relates to IL-22 Fc fusion protein, composition comprising the IL-22 Fc fusion protein, and method of using the composition for the treatment of diseases, especially inflammatory bowel diseases.

Specification includes a Sequence Listing.

IL-22 Amino Acid Sequences Alignment

```
Human (Q9GZX6)              apisshcrldksnfqqpyitnrtfmlakeasladnntdvrligeklfhgvsmsercylmk  60
Chimpanzee (XP_003313906)   apisshcrldkssfqqpyitnrtfmlakeasladnntdvrligeklfhgvsmsercylmk
Orangutan (XP_002823544)    apisshcrldksnfqqpyitnrtfmlakeasladnntdvrligeklfrgvsmsercylmk
Mouse (Q9JJY9)              lpvntrcklevsnfqqpyivnrtfmlakeasladnntdvrligeklfrgvsakdqcylmk
Dog (XP_538274)             lpisshcrldksnfqqpyitnrtfmlakeasladnntdvrligeklfhgvnmgercylml
                             *    * *  * ****** ***************************** **     *****

Human (Q9GZX6)              qvlnftleevlfpqsdrfqpymqevvpflarlsnrlstchiegddlhiqrnvqklkdtvk  120
Chimpanzee (XP_003313906)   qvlnftleevlfpqsdrfqpymqevvpflarlsnrlstchiegddlhiqrnvqklkdtvk
Orangutan (XP_002823544)    qvlnftleevlfpqsdrfqpymqevvpflarlsnrlstchiegddlhiqrnvqklkdtvk
Mouse (Q9JJY9)              qvlnftledvllpqsdrfqpymqevvpfltklsnqlsschisgddqniqknvrrlketvk
Dog (XP_538274)             evlnftleevllpqsdrfqpymqevvpflarlsnklsqchienddghiqrnvqklkdtvq
                             ******* ** ***************** *** ** ***  **  ** **  ** **

Human (Q9GZX6)              klgesgeikaigeldllfmslrnaci  146  (SEQ ID NO:4)
Chimpanzee (XP_003313906)   klgengeikaigeldllfmslrnaci       (SEQ ID NO:48)
Orangutan (XP_002823544)    klgesgeikaigeldllfmslrnaci       (SEQ ID NO:49)
Mouse (Q9JJY9)              klgesgeikaigeldllfmslrnacv       (SEQ ID NO:50)
Dog (XP_538274)             klgengeikaigeldllfmalrnacv       (SEQ ID NO:51)
                            **** ************** *****
```

FIG. 1

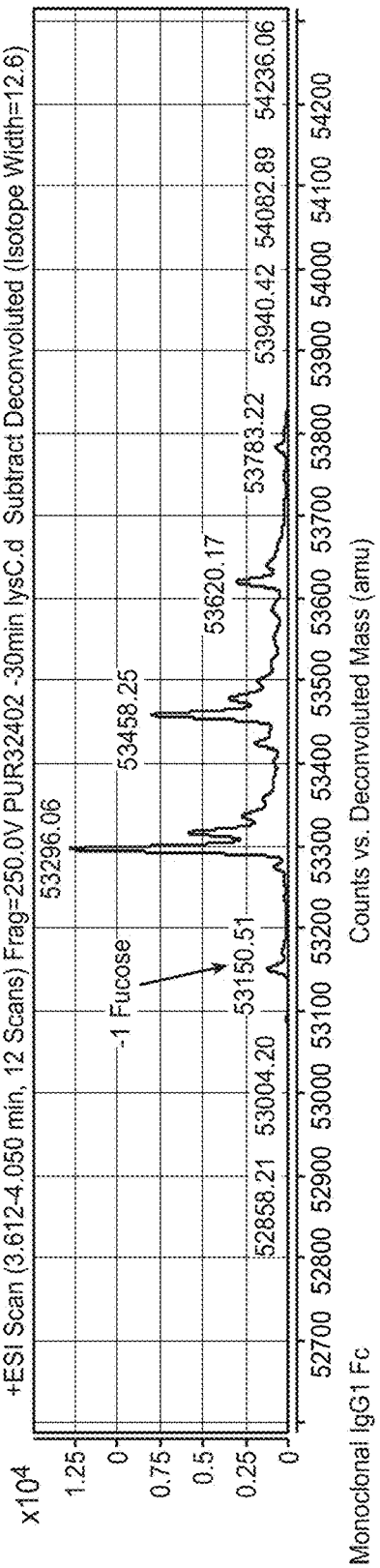

Glycosylation Patterns of the Fc Region
+ESI Scan (3.612-4.050 min, 12 Scans) Frag=250.0V PUR32402 -30min lysC.d Subtract Deconvoluted (Isotope Width=12.6)
x10^4
1.25
0
0.75
0.5
0.25
0
53296.06
53458.25
53620.17
53783.22
53940.42
54082.89
54236.06
-1 Fucose
53150.51
52858.21
53004.20
52700 52800 52900 53000 53100 53200 53300 53400 53500 53600 53700 53800 53900 54000 54100 54200
Monoclonal IgG1 Fc
Counts vs. Deconvoluted Mass (amu)

FIG. 2A

Glycosylation Patterns of the Fc Region
+ESI Scan (3.846-4.045 min, 6 Scans) Frag=250.0V LysC digest IL-22Fc 30 min 27183.d Subtract Deconvoluted (Isotope Width=12.6)
x10^3
6
4
2
0
53295.52
53458.14
53620.10
53782.76
53945.14
-2 Fucose
53003.86
53166.94
-1 Fucose
52801.96
52700 52800 52900 53000 53100 53200 53300 53400 53500 53600 53700 53800 53900 54000 54100 54200
IL-22 IgG1 Fc
EPKSCDKTHT
(SEQ ID NO:33)
Counts vs. Deconvoluted Mass (amu)

FIG. 2B

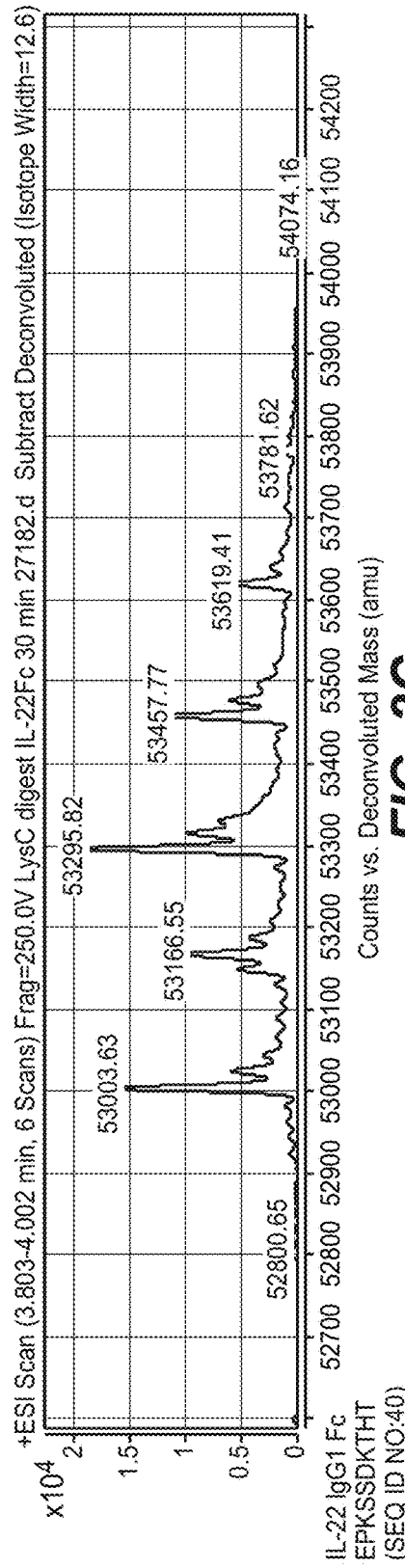

Glycosylation Patterns of the Fc Region
+ESI Scan (3.803-4.002 min, 6 Scans) Frag=250.0V LysC digest IL-22Fc 30 min 27182.d Subtract Deconvoluted (Isotope Width=12.6)
x10^4
2
1.5
1
0.5
0
52800.65
53003.63
53166.55
53295.82
53457.77
53619.41
53781.62
54074.16
52700 52800 52900 53000 53100 53200 53300 53400 53500 53600 53700 53800 53900 54000 54100 54200
Counts vs. Deconvoluted Mass (amu)
IL-22 IgG1 Fc
EPKSSDKTHT
(SEQ ID NO:40)

FIG. 2C

Glycosylation Patterns of the Fc Region
+ESI Scan (3.849-4.048 min, 6 Scans) Frag=250.0V LysC digest IL-22Fc 30 min 25146.d Subtract Deconvoluted (Isotope Width=12.6)
x10^3
6
4
2
0
52801.19
53003.79
53167.04
53295.56
53457.77
53619.84
53781.82
53943.36
52700 52800 52900 53000 53100 53200 53300 53400 53500 53600 53700 53800 53900 54000 54100 54200
Counts vs. Deconvoluted Mass (amu)
IL-22 IgG1 Fc
GGGDKTHT
(SEQ ID NO:41)

FIG. 2D

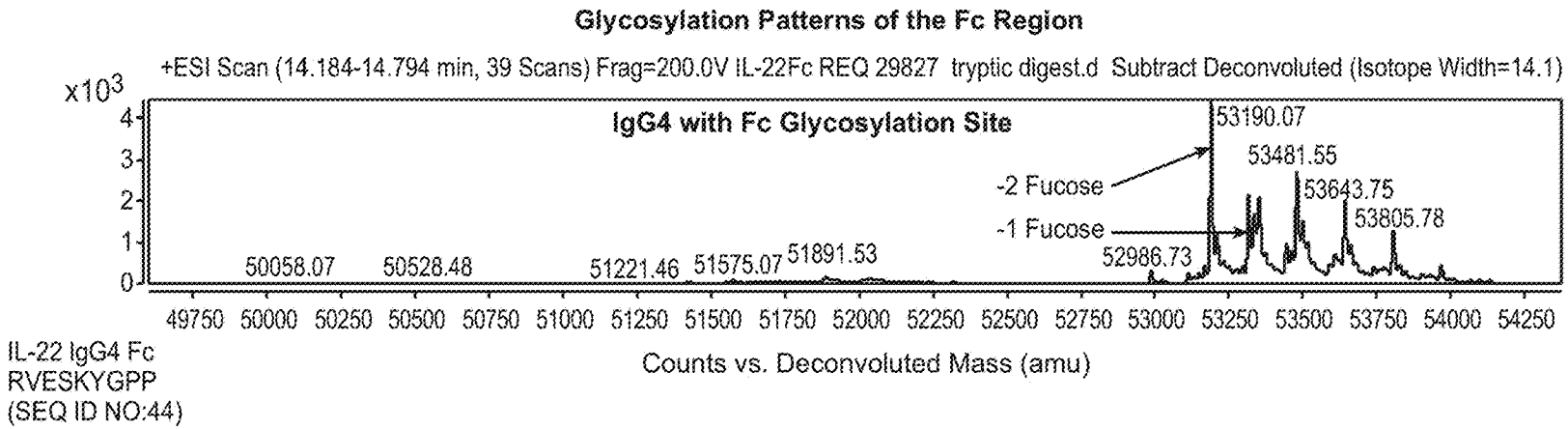

Glycosylation Patterns of the Fc Region
+ESI Scan (14.184-14.794 min, 39 Scans) Frag=200.0V IL-22Fc REQ 29827 tryptic digest.d Subtract Deconvoluted (Isotope Width=14.1)
x10^3
IgG4 with Fc Glycosylation Site
53190.07
53481.55
53643.75
53805.78
-2 Fucose
-1 Fucose
50058.07
50528.48
51221.46
51575.07
51891.53
52986.73
Counts vs. Deconvoluted Mass (amu)
IL-22 IgG4 Fc
RVESKYGPP
(SEQ ID NO:44)

FIG. 2E

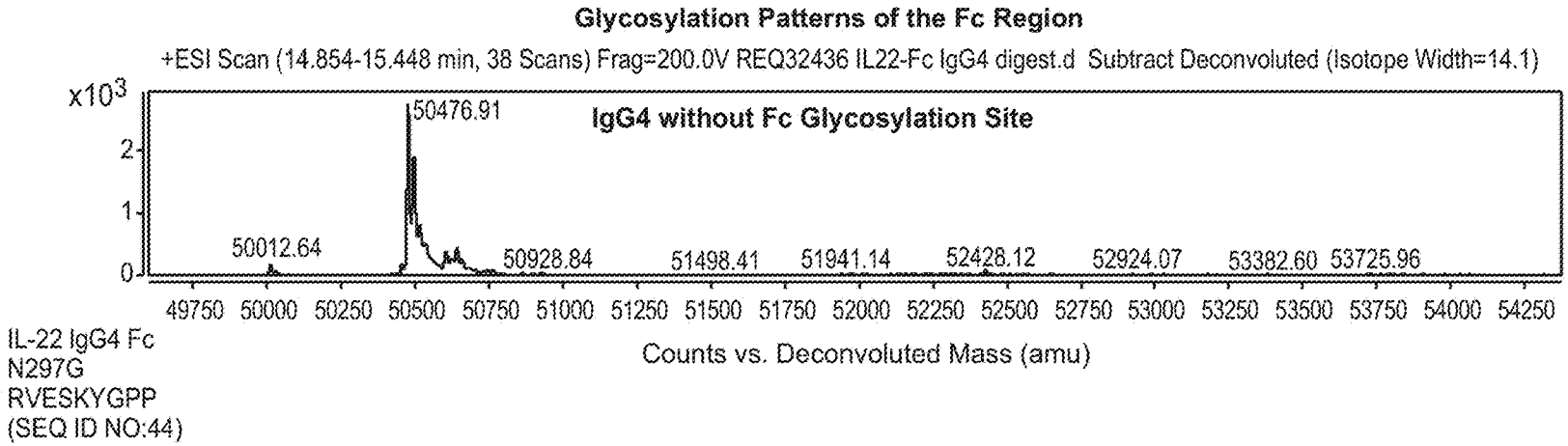

Glycosylation Patterns of the Fc Region
+ESI Scan (14.854-15.448 min, 38 Scans) Frag=200.0V REQ32436 IL22-Fc IgG4 digest.d Subtract Deconvoluted (Isotope Width=14.1)
x10^3
IgG4 without Fc Glycosylation Site
50476.91
50012.64
50928.84
51498.41
51941.14
52428.12
52924.07
53382.60
53725.96
Counts vs. Deconvoluted Mass (amu)
IL-22 IgG4 Fc
N297G
RVESKYGPP
(SEQ ID NO:44)

FIG. 2F

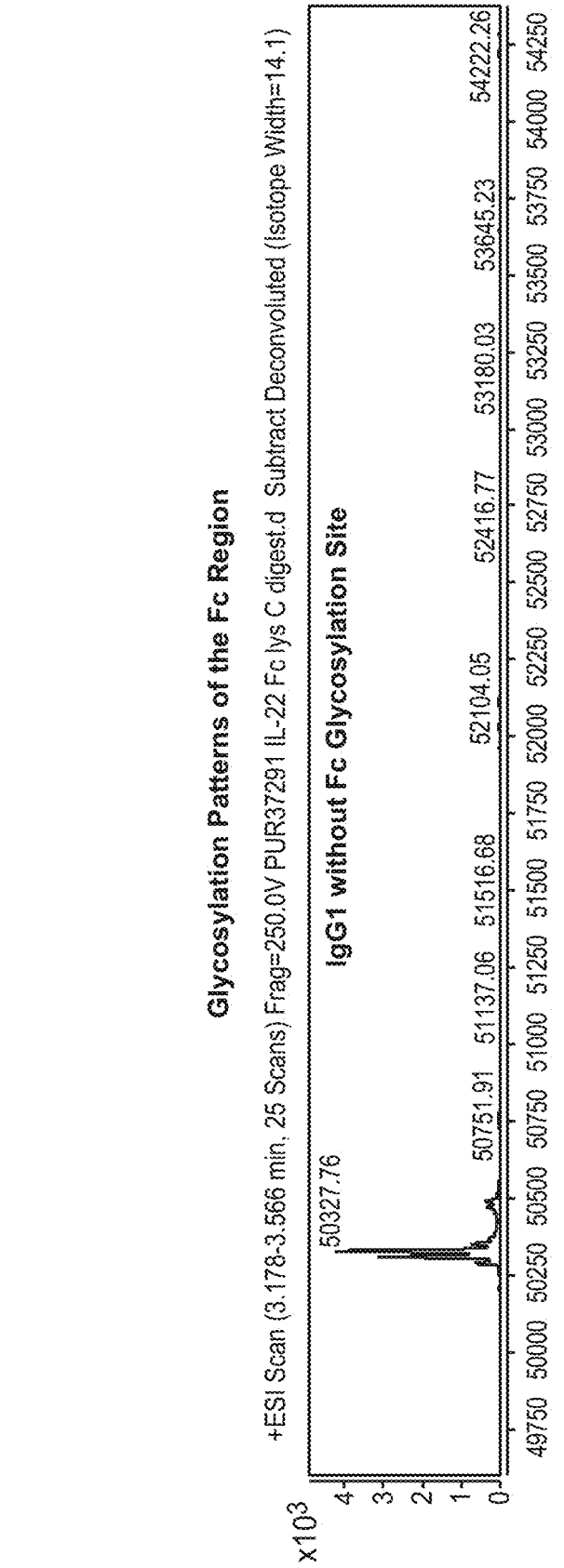

Glycosylation Patterns of the Fc Region
+ESI Scan (3.178-3.566 min, 25 Scans) Frag=250.0V PUR37291 IL-22 Fc lys C digest.d Subtract Deconvoluted (Isotope Width=14.1)
IgG1 without Fc Glycosylation Site
x10^3
4
3
2
1
0
50327.76
50751.91
51137.06
51516.68
52104.05
52416.77
53180.03
53645.23
54222.26
49750 50000 50250 50500 50750 51000 51250 51500 51750 52000 52250 52500 52750 53000 53250 53500 53750 54000 54250
Counts vs. Deconvoluted Mass (amu)
IL-22 IgG1 Fc
N297G
EPKSSDKTHT
(SEQ ID NO:40)

FIG. 2G

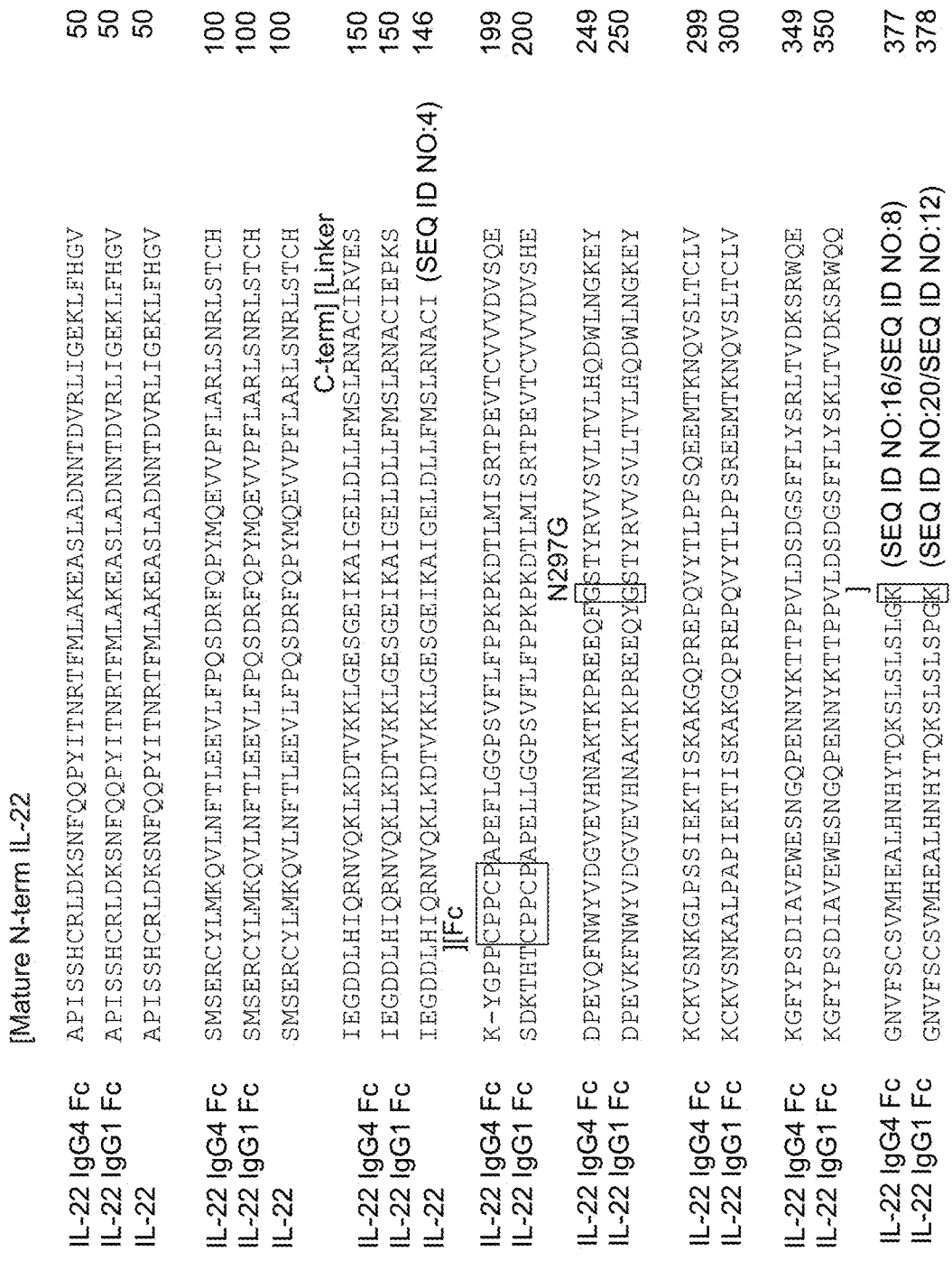

[Mature N-term IL-22
IL-22 IgG4 Fc APISSHCRLDKSNFQQPYITNRTFMLAKEASLADNNTDVRLIGEKLFHGV 50
IL-22 IgG1 Fc APISSHCRLDKSNFQQPYITNRTFMLAKEASLADNNTDVRLIGEKLFHGV 50
IL-22 APISSHCRLDKSNFQQPYITNRTFMLAKEASLADNNTDVRLIGEKLFHGV 50
IL-22 IgG4 Fc SMSERCYLMKQVLNFTLEEVLFPQSDRFQPYMQEVVPFLARLSNRLSTCH 100
IL-22 IgG1 Fc SMSERCYLMKQVLNFTLEEVLFPQSDRFQPYMQEVVPFLARLSNRLSTCH 100
IL-22 SMSERCYLMKQVLNFTLEEVLFPQSDRFQPYMQEVVPFLARLSNRLSTCH 100
C-term] [Linker
IL-22 IgG4 Fc IEGDDLHIQRNVQKLKDTVKKLGESGEIKAIGELDLLFMSLRNACIRVES 150
IL-22 IgG1 Fc IEGDDLHIQRNVQKLKDTVKKLGESGEIKAIGELDLLFMSLRNACIEPKS 150
IL-22 IEGDDLHIQRNVQKLKDTVKKLGESGEIKAIGELDLLFMSLRNACI (SEQ ID NO:4) 146
][Fc
IL-22 IgG4 Fc K-YGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQE 199
IL-22 IgG1 Fc SDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE 200
N297G
IL-22 IgG4 Fc DPEVQFNWYVDGVEVHNAKTKPREEQFGSTYRVVSVLTVLHQDWLNGKEY 249
IL-22 IgG1 Fc DPEVKFNWYVDGVEVHNAKTKPREEQYGSTYRVVSVLTVLHQDWLNGKEY 250
IL-22 IgG4 Fc KCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLV 299
IL-22 IgG1 Fc KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV 300
IL-22 IgG4 Fc KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQE 349
IL-22 IgG1 Fc KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ 350
]
IL-22 IgG4 Fc GNVFSCSVMHEALHNHYTQKSLSLSLGK (SEQ ID NO:16/SEQ ID NO:8) 377
IL-22 IgG1 Fc GNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:20/SEQ ID NO:12) 378

FIG. 3

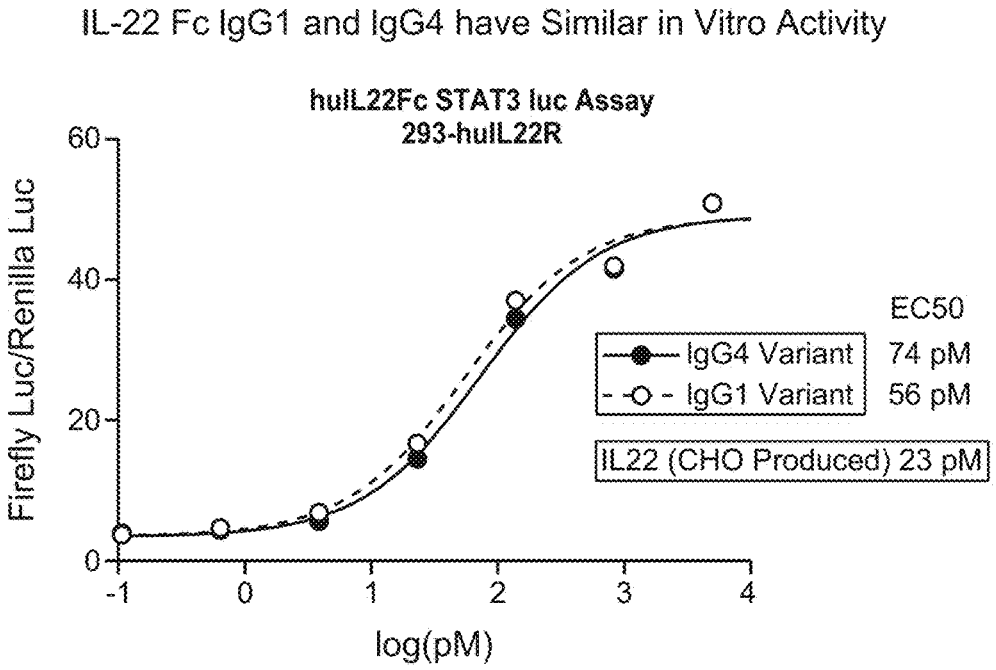

IL-22 Fc IgG1 and IgG4 have Similar in Vitro Activity
huIL22Fc STAT3 luc Assay
293-huIL22R
Firefly Luc/Renilla Luc
log(pM)
EC50
IgG4 Variant 74 pM
IgG1 Variant 56 pM
IL22 (CHO Produced) 23 pM

FIG. 4

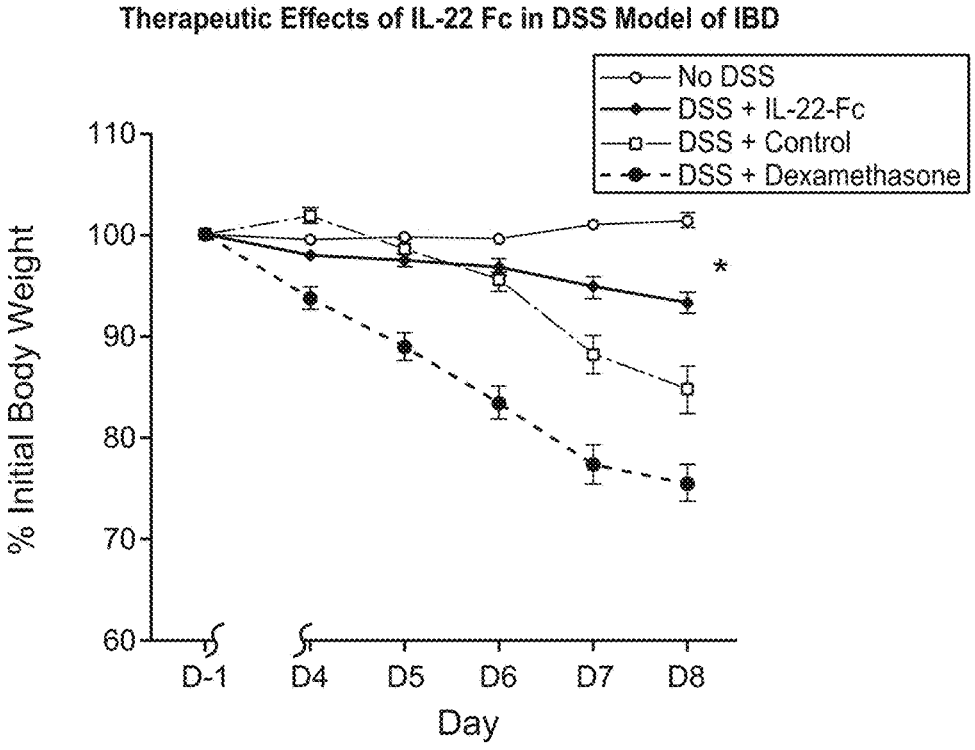
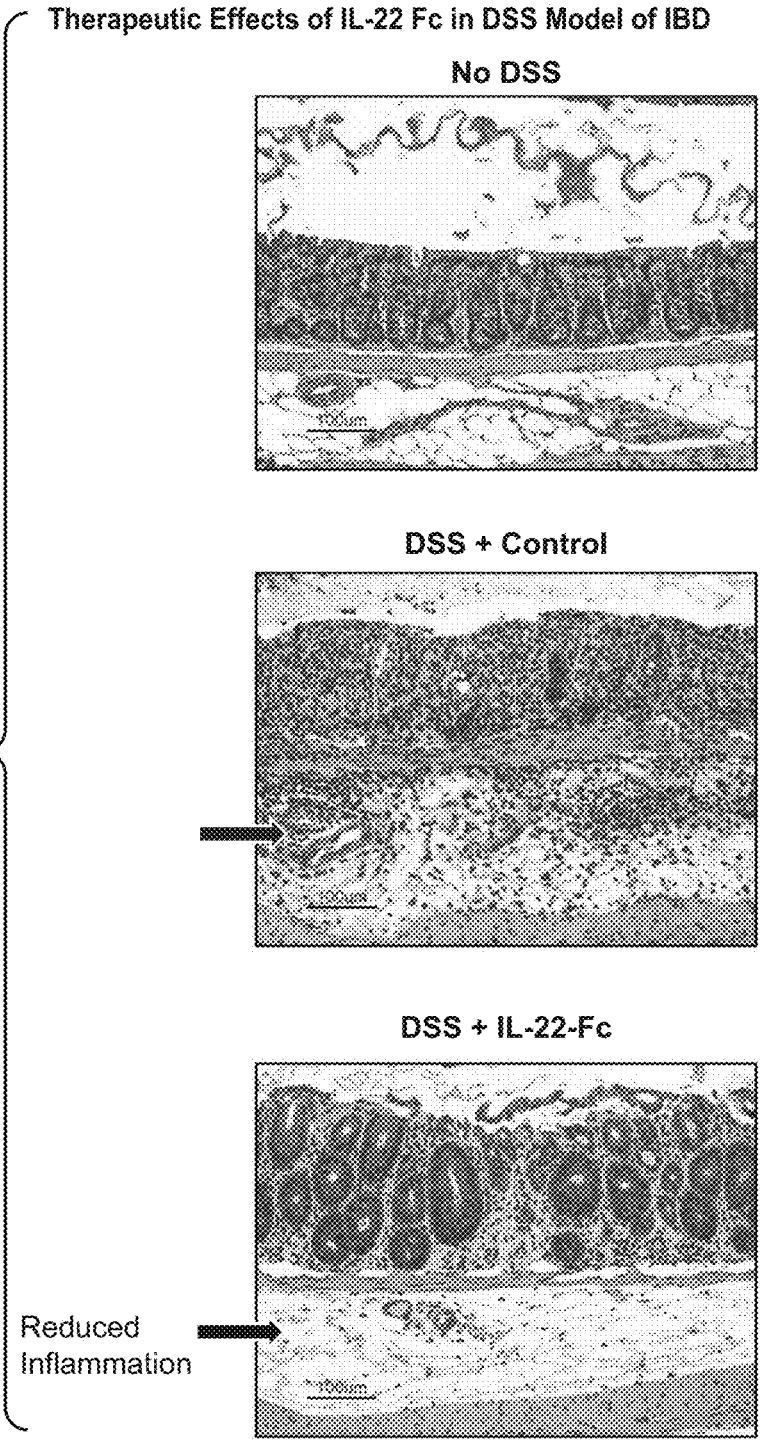

Therapeutic Effects of IL-22 Fc in DSS Model of IBD
No DSS
DSS + IL-22-Fc
DSS + Control
DSS + Dexamethasone
% Initial Body Weight
Day
D-1
D4
D5
D6
D7
D8
*

FIG. 5A

FIG. 5B


Therapeutic Effects of IL-22 Fc in DSS Model of IBD
No DSS
DSS + Control
DSS + IL-22-Fc
Reduced Inflammation

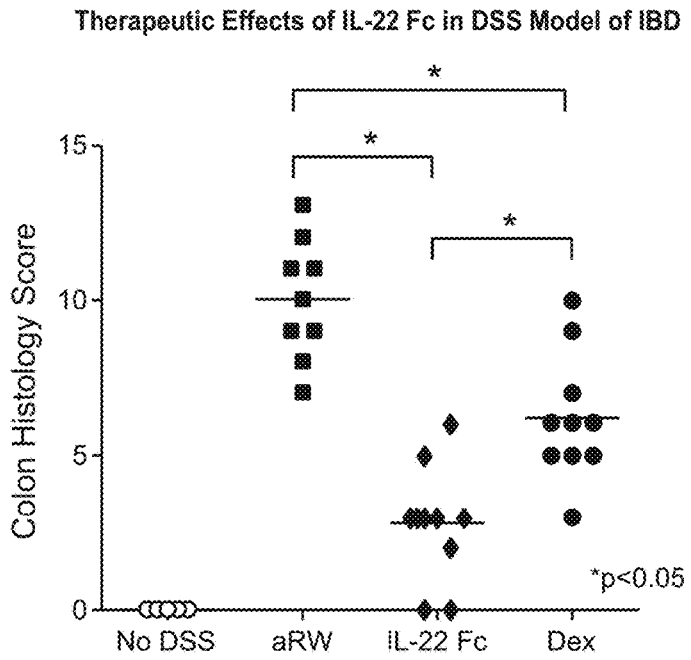

Therapeutic Effects of IL-22 Fc in DSS Model of IBD
Colon Histology Score
15
10
5
0
*
*
*
*p<0.05
No DSS
aRW
IL-22 Fc
Dex

FIG. 5C

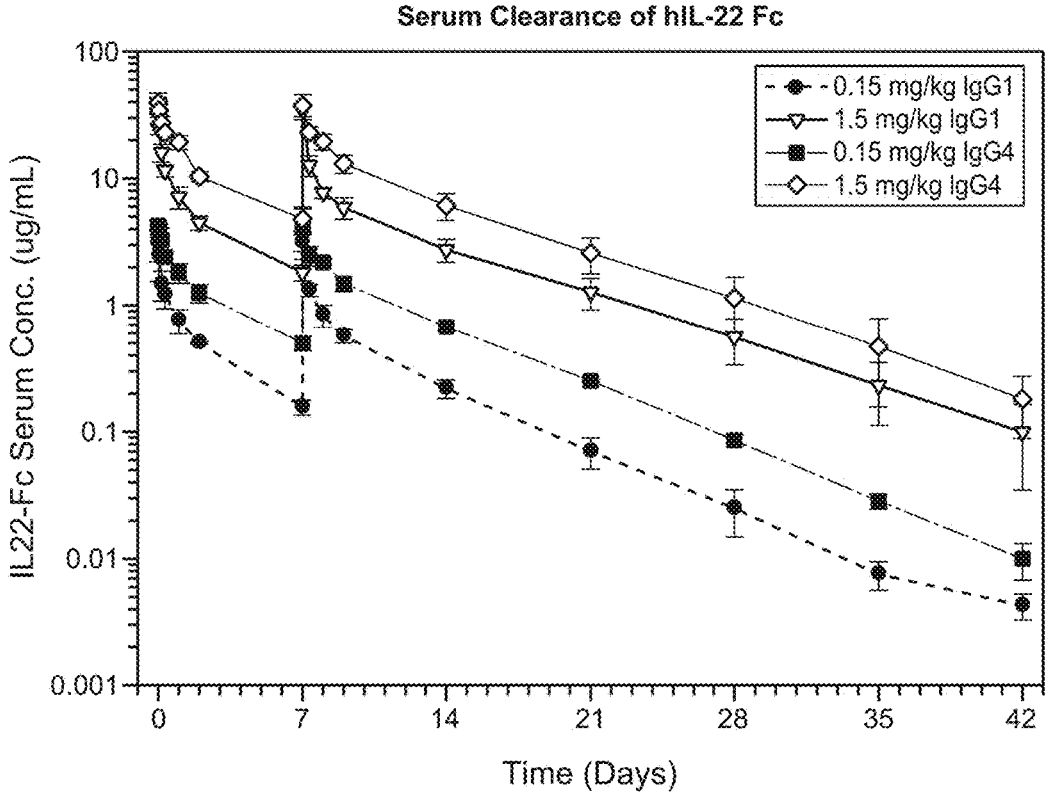
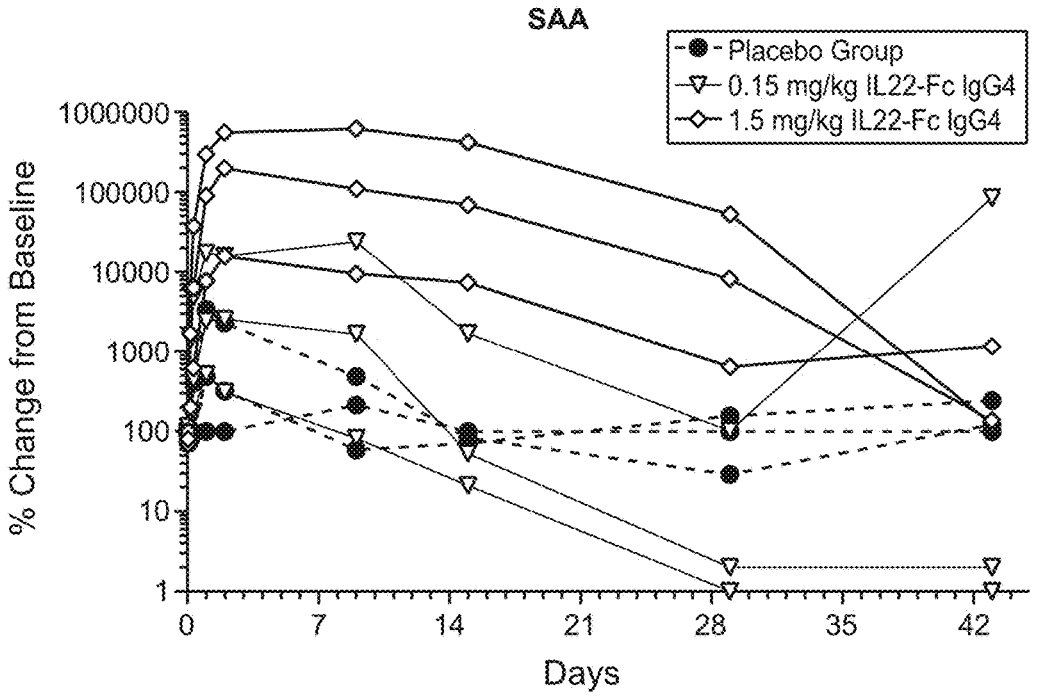

Serum Clearance of hIL-22 Fc
IL22-Fc Serum Conc. (ug/mL)
100
10
1
0.1
0.01
0.001
0
7
14
21
28
35
42
Time (Days)
0.15 mg/kg IgG1
1.5 mg/kg IgG1
0.15 mg/kg IgG4
1.5 mg/kg IgG4

FIG. 6


SAA
Placebo Group
0.15 mg/kg IL22-Fc IgG4
1.5 mg/kg IL22-Fc IgG4
% Change from Baseline
1000000
100000
10000
1000
100
10
1
0
7
14
21
28
35
42
Days

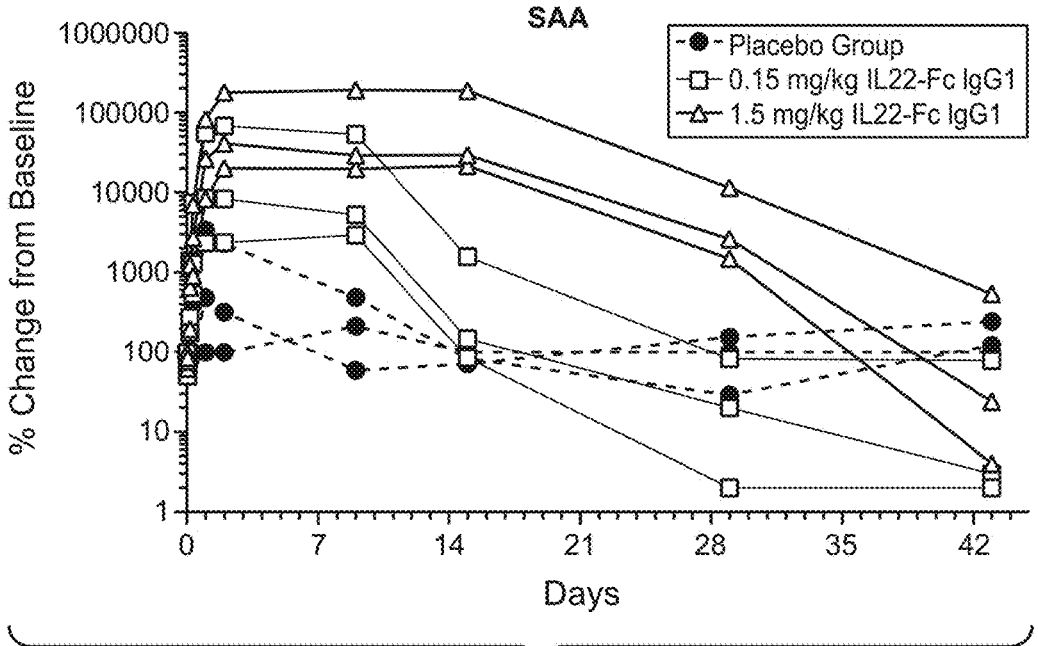
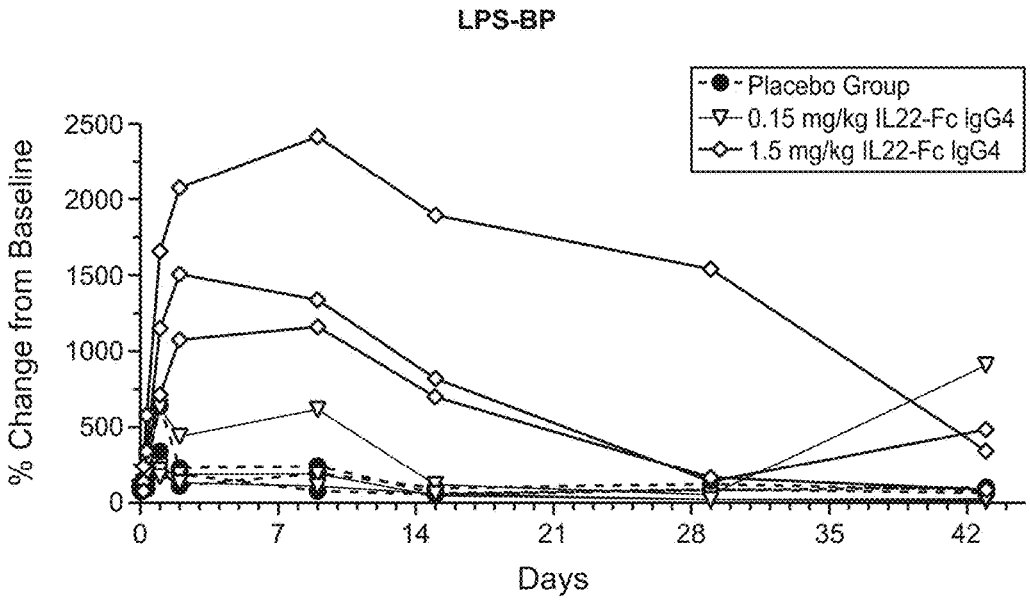

SAA
Placebo Group
0.15 mg/kg IL22-Fc IgG1
1.5 mg/kg IL22-Fc IgG1
% Change from Baseline
1000000
100000
10000
1000
100
10
1
0
7
14
21
28
35
42
Days

FIG. 7A


LPS-BP
Placebo Group
0.15 mg/kg IL22-Fc IgG4
1.5 mg/kg IL22-Fc IgG4
% Change from Baseline
2500
2000
1500
1000
500
0
0
7
14
21
28
35
42
Days

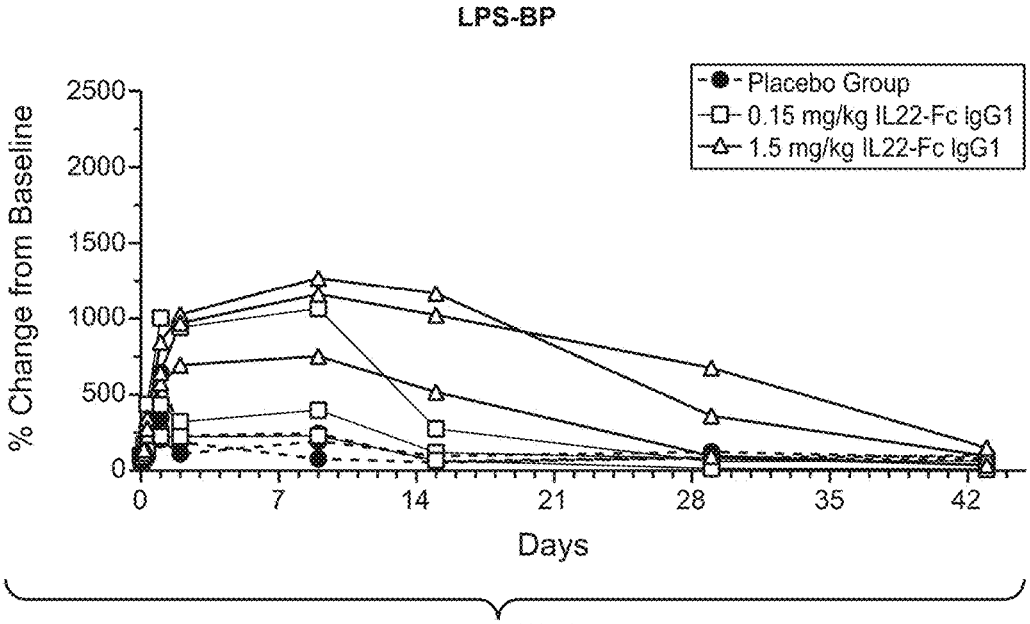
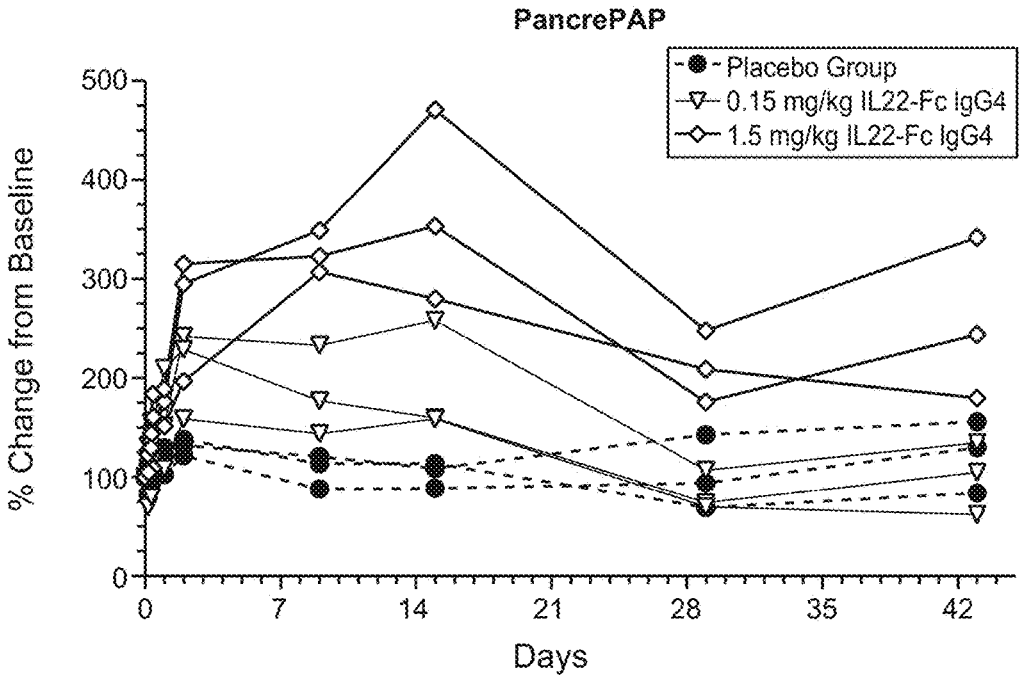

LPS-BP
Placebo Group
0.15 mg/kg IL22-Fc IgG1
1.5 mg/kg IL22-Fc IgG1
% Change from Baseline
2500
2000
1500
1000
500
0
0
7
14
21
28
35
42
Days

FIG. 7B


PancrePAP
Placebo Group
0.15 mg/kg IL22-Fc IgG4
1.5 mg/kg IL22-Fc IgG4
% Change from Baseline
500
400
300
200
100
0
0
7
14
21
28
35
42
Days

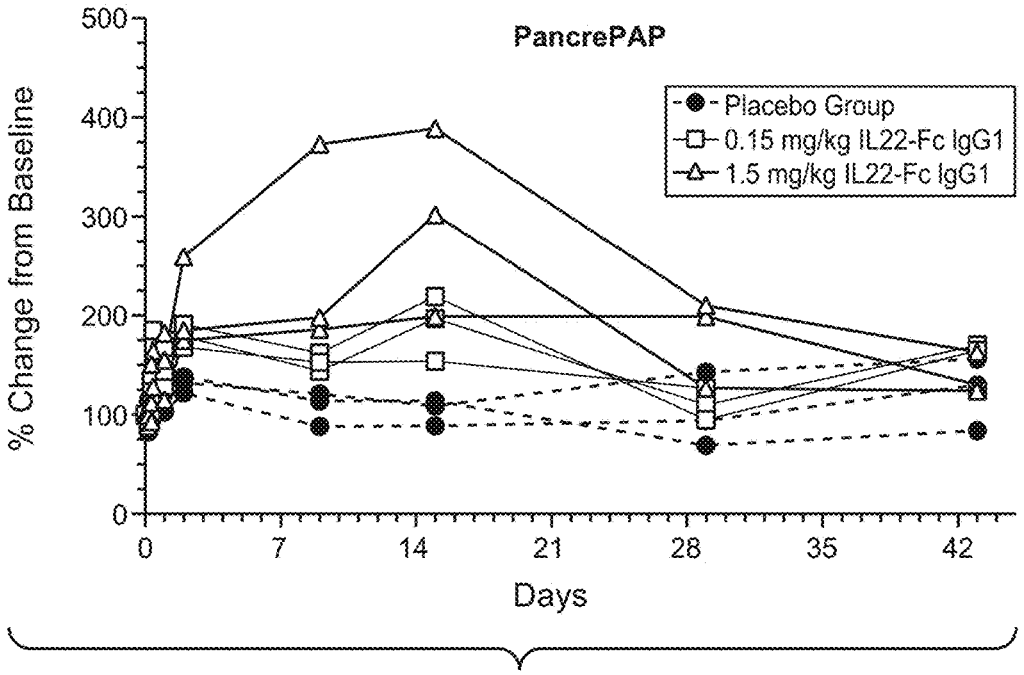

PancrePAP
Placebo Group
0.15 mg/kg IL22-Fc IgG1
1.5 mg/kg IL22-Fc IgG1
% Change from Baseline
500
400
300
200
100
0
0
7
14
21
28
35
42
Days

FIG. 7C

IL-22 FC FUSION PROTEIN AND METHODS OF USE

[0001] This application is a continuation of U.S. Ser. No. 15/842,493, which was filed on Dec. 14, 2017, which is a continuation of U.S. Ser. No. 15/588,103, which was filed on May 5, 2017, which is a continuation of U.S. Ser. No. 15/276,511, which was filed on Sep. 26, 2016, which is a continuation of U.S. Ser. No. 15/019,845, which was filed on Feb. 9, 2016, which is a continuation of U.S. Ser. No. 14/751,251, which was filed on Jun. 26, 2015, which is a continuation of U.S. Ser. No. 14/535,579, which was filed on Nov. 7, 2014, which is a continuation of U.S. Ser. No. 14/216,802, which was filed on Mar. 17, 2014, and claims benefit of priority under 35 U.S.C. 119 to U.S. provisional application Ser. No. 61/800,148, Ser. No. 61/800,795 and Ser. No. 61/801,144, all of which were filed on Mar. 15, 2013. The contents of all of the above applications are incorporated herein by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing submitted via EFS-Web and hereby incorporated by reference in its entirety. Said ASCII copy, created on Dec. 7, 2017, is named 50474-1350024_Sequence_Listing_12.7.17_ST25 and is 89,299 bytes in size.

FIELD OF THE INVENTION

[0003] The present invention relates to IL-22 Fc fusion proteins, compositions comprising the same, and methods of making and method of using the same.

BACKGROUND

[0004] Interleukin-22 (IL-22) is a member of the IL-10 family of cytokine that is produced by Th22 cells, NK cells, lymphoid tissue inducer (LTi) cells, dendritic cells and Th17 cells. IL-22 binds to the IL-22R1/IL-10R2 receptor complex, which is expressed in innate cells such as epithelial cells, hepatocytes, and keratinocytes.

[0005] IL-22 plays an important role in mucosal immunity, mediating early host defense against attaching and effacing bacterial pathogens. See Zheng et al., 2008, Nat. Med. 14:282-89. IL-22 promotes the production of antimicrobial peptides and proinflammatory cytokines from epithelial cells and stimulates proliferation and migration of colonic epithelial cells in the gut. See Kumar et al., 2013, J. Cancer, 4:57-65. Upon bacterial infection, IL-22 knock-out mice displayed impaired gut epithelial regeneration, high bacterial load and increased mortality. Kumar et al., supra. Similarly, infection of IL-22 knock-out mice with influenza virus resulted in severe weight loss and impaired regeneration of tracheal and bronchial epithelial cells. Thus, IL-22 plays a pro-inflammatory role in suppressing microbial infection as well as an ant-inflammatory protective role in epithelial regeneration in inflammatory responses. The seemingly conflicting reports on the effects of IL-22 on epithelial cells are not yet thoroughly understood. Kumar et al., supra.

[0006] Increased expression of IL-22 is detected in inflammatory bowel disorder (IBD) patients. See e.g., Wolk et al., 2007, J. Immunology, 178:5973; Andoh et al., 2005, Gastroenterology, 129:969. IBDs such as Crohn's disease (CD) and ulcerative colitis (UC) are thought to result from a dysregulated immune response to the commensal microflora present in the gut. Cox et al., 2012, Mucosal Immunol. 5:99-109. Both UC and CD are complex diseases that occur in genetically susceptible individuals who are exposed to as yet poorly-defined environmental stimuli. CD and UC are mediated by both common and distinct mechanisms and exhibit distinct clinical features. See Sugimoto et al. 2008, J. Clinical Investigation, 118:534-544.

[0007] In UC, inflammation occurs primarily in the mucosa of the colon and the rectum, leading to debilitating conditions including diarrhea, rectal bleeding, and weight loss. It is thought that UC is largely caused by an inappropriate inflammatory response by the host to intestinal microbes penetrating through a damaged epithelial barrier (Xavier and Podolsky, 2007, Nature 448:427-434). Crohn's disease is characterized by intestinal infilatratoin of activated immune cells and distortion of the intestinal architechture. See Wolk et al., supra.

[0008] In recent years, a number of drugs based on various strategies to regulate the immune response have been tested to treat IBD, including steroids, immunomodulators, and antibodies against inflammatory cytokines, with variable success (Pastorelli et al., Expert opinion on emerging drugs, 2009, 14:505-521). The complex variety of gut flora contributes to the heterogeneity of the disease. Thus, there is a need for a better therapeutics for IBD.

SUMMARY

[0009] The invention provides IL-22 Fc fusion protein, compositions comprising the same, and methods of using the same.

[0010] In one aspect, the invention provides an IL-22 Fc fusion protein that binds to IL-22 receptor, said IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, wherein the IL-22 Fc fusion protein comprises an amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, preferably at least 99% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO: 10, SEQ ID NO: 12 and SEQ ID NO: 14, and wherein the Fc region is not glycosylated. In certain embodiments, the N297 residue of the CH2 domain is changed to glycine or alanine. In certain other embodiments, the N297 residue is changed to Gly; while in other embodiments, the N297 residue is changed to Ala.

[0011] In certain embodiments, the IL-22 Fc fusion protein comprises an amino acid sequence having at least 98% sequence identity to the amino acid sequence of SEQ ID NO:8 or SEQ ID NO: 12. In certain other embodiments, the IL-22 Fc fusion protein comprises an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8 or SEQ ID NO: 12. In certain other embodiments, the IL-22 Fc fusion protein comprises an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8. In certain other embodiments, the IL-22 Fc fusion protein comprises an amino acid sequence having at least 99% sequence identity to the amino acid sequence of SEQ ID NO: 12. In certain embodiments, the functions and/or activities of the IL-22 Fc fusion protein can be assayed by in vitro or in vivo methods, for example, IL-22 receptor binding assay, Stat3 luciferase reporter activity assay, etc. In certain

embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO: 12. In certain particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8. In certain embodiments, the invention provides the IL-22 Fc fusion protein produced by the method comprising the step of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein. In certain embodiments, the method further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium. In certain embodiments, the host cell is a Chinese hamster ovary (CHO) cell; while in other embodiments, the host cell is an *E. coli* cell.

[0012] In another aspect, the invention provides an IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an IgG Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, and wherein the Fc region is not glycosylated. In certain embodiments, the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31). In certain other embodiments, the N297 residue in the Fc region is changed and/or the T299 residue in the Fc region is changed. In certain embodiments, the N297 residue in the CH2 domain is changed, preferably to glycine or alanine. In certain particular embodiments, the N297 residue is changed to glycine. In certain other embodiments, the N297 residue is changed to alanine. In yet other embodiments, the T299 residue is changed to Ala, Gly or Val. In certain other embodiments, the linker is 8-20 amino acids long, 8-16 amino acids long, or 10-16 amino acids long.

[0013] In certain embodiments, the Fc region comprises the CH2 and CH3 domain of IgG. In certain particular embodiments, the linker comprises the amino acid sequence DKTHT (SEQ ID NO:32). In certain embodiments, the linker comprises the amino acid sequence GGGDKTHT (SEQ ID NO:41). In certain embodiments, the linker is at least 11 amino acids long and comprises the amino acid sequence EPKSCDKTHT (SEQ ID NO:33). In certain other embodiments, the linker comprises the amino acid sequence VEPKSCDKTHT (SEQ ID NO:34), KVEPKSCDKTHT (SEQ ID NO:35), KKVEPKSCDKTHT (SEQ ID NO:36), DKKVEPKSCDKTHT (SEQ ID NO:37), VDKKVEPKSCDKTHT (SEQ ID NO:38), or KVDKKVEPKSCDKTHT (SEQ ID NO:39). In certain particular embodiments, the linker comprises the amino acid sequence EPKSSDKTHT (SEQ ID NO:40). In certain embodiments, the linker comprises the amino acid sequence VEPKSSDKTHT (SEQ ID NO:67), KVEPKSSDKTHT (SEQ ID NO:68), KKVEPKSSDKTHT (SEQ ID NO:66), DKKVEPKSSDKTHT (SEQ ID NO:64), VDKKVEPKSSDKTHT (SEQ ID NO:69), or KVDKKVEPKSSDKTHT (SEQ ID NO:65). In certain particular embodiments, the linker does not comprise the amino acid sequence of GGS (SEQ ID NO: 45, GGGS (SEQ ID NO:46) or GGGGS (SEQ ID NO:47). In separate embodiments, the IL-22 IgG1 Fc fusion protein comprises a linker sequence of GGGSTHT (SEQ ID NO:63). In other particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO: 12 or SE ID NO: 14. In certain other particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO: 12.

[0014] In certain embodiments, the IL-22 Fc fusion protein comprises the CH2 and CH3 domain of IgG4. In certain other embodiments, the linker comprises the amino acid sequence SKYGPP (SEQ ID NO:43). In certain particular embodiments, the linker comprises the amino acid sequence RVESKYGPP (SEQ ID NO:44). In certain embodiments, none of the linkers comprise the amino acid sequence GGS (SEQ ID NO:45), GGGS (SEQ ID NO:46) or GGGGS (SEQ ID NO:47). In other particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8 or SE ID NO: 10. In particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8. In another embodiment, the IL-22 Fc fusion protein is produced by the method comprising the step of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein. In certain embodiments, the IL-22 Fc fusion protein is produced by the method that further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium. In certain embodiments, the host cell is a Chinese hamster ovary (CHO) cell. In certain other embodiments, the host cell is an *E. coli* cell.

[0015] In yet another aspect, the invention provides a composition comprising an IL-22 Fc fusion protein, said IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, and wherein the composition has an afucosylation level in the CH2 domain of no more than 5%. In certain embodiments, the afucosylation level is no more than 2%, more preferably less than 1%. In certain embodiments, the afucosylation level is measured by mass spectrometry. In certain embodiments, the Fc region comprises the CH2 and CH3 domain of IgG4. In certain embodiments, the Fc region comprises a CH2 and CH3 domain of IgG. In certain other embodiments, the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31). In certain embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26. In certain embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24. In certain embodiments, the composition is produced by the process comprising the steps of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein, and obtaining the IL-22 Fc fusion protein from the cell culture or culture medium, wherein the composition has an afucosylation level in the CH2 domain of the Fc region of no more than 5%. In certain embodiments, the afucosylation level is no more than 2%, more preferably less than 1%. In certain embodiments, the IL-22 Fc fusion protein is obtained by purification, preferably purifying fucosylated species away from afucosylated species. In certain embodiments, the IL-22 Fc fusion protein is purified by affinity chromatography. In certain embodiments, the host cell is a CHO cell.

[0016] In a further aspect, the invention provides an IL-22 Fc fusion protein, or a composition comprising IL-22 Fc fusion proteins, said IL-22 Fc fusion protein is produced by the process comprising the step of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein. In certain embodiments, the process further comprises the step of obtaining the IL-22 Fc fusion protein from

the cell culture or culture medium. In certain embodiments, the host cell is a CHO cell; while in other embodiments, the host cell is an *E. coli* cell.

[0017] In a further aspect, the invention provides a composition comprising an IL-22 Fc fusion protein described herein. In yet another aspect, the invention provides a pharmaceutical composition comprising an IL-22 Fc fusion protein described herein, and at least one pharmaceutically acceptable carrier. In certain embodiments, the composition or pharmaceutical composition comprises an IL-22 Fc fusion protein comprising an amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:24 or SEQ ID NO:26. In certain particular embodiments, the composition or pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8. In certain particular embodiments, the IL-22 Fc fusion protein is produced by *E. coli*. In certain other embodiments, the Fc region of the IL-22 Fc fusion protein is not glycosylated. In certain further embodiments, the IL-22 Fc fusion protein does not induce antibody dependent cellular cytotoxicity. In certain embodiments, the pharmaceutical composition further comprises a suboptimal amount of a therapeutic such as dexamethasone. In certain embodiments, the IL-22 polypeptide comprises the amino acid sequence of SEQ ID NO:4.

[0018] Further, according to each and every aspect of the invention, in certain embodiments, the IL-22 Fc fusion protein can be a dimeric IL-Fc fusion protein (with respect to IL-22); while in other embodiments, the IL-22 Fc fusion protein can be a monomeric Fc fusion protein (with respect to IL22).

[0019] In a further aspect, the invention provides a monomeric IL-22 Fc fusion protein. In certain particular embodiments, the monomeric fusion protein comprises an IL-22 Fc fusion arm and an Fc arm. In certain embodiments, the IL-22 Fc fusion arm and the Fc arm comprises either a knob or a hole in the Fc region. In certain embodiments, the Fc region of the IL-22 Fc fusion arm (the monomer IL-22 Fc fusion) comprises a knob and the Fc region of the Fc arm (the monomer Fc without linking to IL-22) comprises a hole. In certain other embodiments, the monomeric IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:61 and SEQ ID NO:62. In certain other embodiments, the Fc region of both arms further comprises an N297G mutation. In certain embodiments, the monomeric IL-22 Fc is produced by the process comprising the step of culturing one or more host cells comprising one or more nucleic acid molecules capable of expressing the first polypeptide comprising the amino acid sequence of SEQ ID NO:61 and the second polypeptide comprising the amino acid sequence of SEQ ID NO:62. In certain other embodiments, the method further comprises the step of obtaining the monomeric IL-22 Fc fusion protein from the cell culture or culture medium. In certain embodiments, the host cell is an *E. coli* cell. In a related aspect, the invention provides a composition or pharmaceutical composition comprising the monomeric IL-22 Fc fusion protein.

[0020] In yet another aspect, the invention provides an isolated nucleic acid encoding the IL-22 Fc fusion protein described herein. In certain embodiments, the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8, SEQ ID NO: 10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:24 or SEQ ID NO:26, preferably SEQ ID NO:8 or SEQ ID NO: 12, more preferably SEQ ID NO:8. In certain other embodiments, the nucleic acid comprises the polynucleotide sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO: 11, SEQ ID NO: 13, SEQ ID NO:23 or SEQ ID NO:25. In certain particular embodiments, the nucleic acid comprises the polynucleotide sequence of SEQ ID NO:7 or SEQ ID NO: 11, preferably SEQ ID NO:7. In related aspects, the invention provides vectors comprising the nucleic acid described above, and a host cell comprising the vector. In certain embodiments, the host cell is a prokaryotic cell or eukaryotic cell. In certain particular embodiments, the host cell is a prokaryotic cell, including without limitation, an *E. coli* cell. In certain other embodiments, the host cell is a eukaryotic cell, including without limitation, a CHO cell. In certain embodiments, the host cell comprises a vector comprising a nucleic acid encoding the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

[0021] In a further related aspect, the invention provides methods of making the IL-22 Fc fusion protein comprising the step of culturing the host cell under conditions suitable for expression of the IL-22 Fc fusion protein. In certain embodiments, the method further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium. The IL-22 Fc fusion protein can be obtained from the cell culture or culture medium by any methods of protein isolation or purification known in the art, including without limitation, collecting culture medium, freezing/thawing, centrifucation, cell lysis, homogenization, ammonium sulfate precipitation, HPLC, and affinity, gel filtration, and ion exchanger column chromatography. In certain embodiments, the method further comprises the step of removing afucosylated IL-22 Fc fusion protein. In certain other embodiments, the afucosylated IL-22 Fc fusion protein is removed by affinity column chromatography. In certain embodiments, the host cell is an *E. coli* cell. In other embodiments, the host cell is a CHO cell.

[0022] In yet another aspect, the invention provides a composition or pharmaceutical composition comprising an IL-22 Fc fusion protein of the invention and at least one pharmaceutically acceptable carrier. In certain embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:24, or SEQ ID NO:26. In other embodiments, the Fc region of the IL-22 Fc fusion protein is not glycosylated. In certain embodiments, the IL-22 Fc fusion protein does not induce antibody dependent cellular cytotoxicity. In yet other embodiments, the pharmaceutical composition further comprises dexamethasone or a TNF antagonist. In certain particular embodiments, the dexamethasone or a TNF antagonist is present at a suboptimal amount.

[0023] In another aspect, the invention provides methods of treating IBD in a subject in need thereof comprising administering to the subject the pharmaceutical composition comprising an IL-22 Fc fusion protein of the invention. In certain embodiments, the IBD is ulcerative colitis. In certain other embodiments, the IBD is Crohn's disease. In certain particular embodiments, the Fc region of the IL-22 Fc fusion protein is not glycosylated. In certain embodiments, the N297 residue and/or the T299 residue of the Fc region is changed. In certain embodiments, the N297 residue of the Fc region is changed. In certain other embodiments, the N297 residue is changed to Gly or Ala, preferably Gly. In certain other embodiments, the T299 residue is changed, preferably

to Val, Gly or Ala. In certain particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8, SEQ ID NO: 10, SEQ ID NO: 12 or SEQ ID NO: 14, preferably SEQ ID NO:8. In certain embodiments, the IL-22 Fc fusion protein is produced in *E. coli*. In certain embodiments, the subject is a human. In certain other embodiments, the pharmaceutical composition is administered intravenously, subcutaneously or topically.

[0024] In another aspect, the invention provides methods of treating any one or combination of the following diseases using an IL-22 Fc fusion protein of this invention: Type II diabetes, wounds (including diabetic wounds and diabetic ulcers), graft versus host disease (GVHD), pancreatitis, atherosclerosis, cardiovascular disease, metabolic syndrome, endotoxemia (acute and mild), sepsis, acute coronary heart disease, hypertenson, dyslipemia, obesity, hyperglycemia. In some further embodiments, the patient to be treated for the above disease is in need of a change in his HDL/LDL lipid profile, which IL-22 Fc fusion proteins can alter in the patient to increase HDL and decrease LDL.

[0025] In certain other embodiments, the pharmaceutical composition comprising IL-22 Fc fusion proteins has an afucosylation level in the CH2 domain of no more than 5%, preferably no more than 2%, more preferably less than 1%. In certain particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26, preferably SEQ ID NO:24. In certain other embodiments, the IL-22 Fc fusion protein is produced in CHO cells. In certain particular embodiments, the subject is a human. In certain other embodiments, the pharmaceutical composition is administered intravenously, subcutaneously or topically.

[0026] In a further aspect, the invention provides methods of inhibiting microbial infection in the intestine, or preserving goblet cells in the intestine during a microbial infection, of a subject in need thereof comprising the step of administering to the subject the pharmaceutical comprising the IL-22 Fc fusion protein of the invention. In other related aspects, the invention provides methods of enhancing epithelial cell integrity, epithelial cell proliferation, epithelial cell differentiation, epithelial cell migration or epithelial wound healing in the intestine in a subject in need thereof comprising administering to the subject the pharmaceutical composition comprising the IL-22 Fc fusion protein of the invention. In certain embodiments, the epithelial cell is intestinal epithelial cell.

[0027] In certain embodiments of these aspects, the Fc region of the IL-22 Fc fusion protein is not glycosylated. In certain embodiments, the N297 residue and/or the T299 residue of the Fc region is changed. In certain embodiments, the N297 residue of the Fc region is changed. In certain other embodiments, the N297 residue is changed to Gly or Ala, preferably Gly. In certain other embodiments, the T299 residue is changed, preferably to Val, Gly or Ala. In certain particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12 or SEQ ID NO:14, preferably SEQ ID NO:8. In certain embodiments, the IL-22 Fc fusion protein is produced in *E. coli*. In certain embodiments, the subject is a human. In certain other embodiments, the pharmaceutical composition is administered intravenously, subcutaneously or topically.

[0028] In certain other embodiments, the pharmaceutical composition comprising IL-22 Fc fusion proteins has an afucosylation level in the CH2 domain of no more than 5%, preferably no more than 2%, more preferably less than 1%. In certain particular embodiments, the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26, preferably SEQ ID NO:24. In certain other embodiments, the IL-22 Fc fusion protein is produced in CHO cells. In certain particular embodiments, the subject is a human. In certain other embodiments, the pharmaceutical composition is administered intravenously, subcutaneously or topically.

[0029] In yet other embodiments of the above aspects, the N-glycan attached to the Fc region of the IL-22 Fc fusion protein is enzymatically removed by a glycolytic enzyme. In certain embodiments, glycolytic enzyme is peptide-N-glycosidase (PNGase). In certain particular embodiments, the subject is a human.

[0030] In yet a further aspect, the invention also provides uses of an IL-22 Fc fusion protein described herein in the preparation of a medicament for the treatment of IBD, including UC and CD, in a subject in need thereof. In a related aspect, the invention provides uses of an IL-22 Fc fusion protein described herein in the preparation of a medicament for inhibiting microbial infection in the intestine, or preserving goblet cells in the intestine during a microbial infection in a subject in need thereof. In yet another aspect, the invention provides uses of an IL-22 Fc fusion protein described herein in the preparation of a medicament for enhancing epithelial cell integrity, epithelial cell proliferation, epithelial cell differentiation, epithelial cell migration or epithelial wound healing in the intestine, in a subject in need thereof.

[0031] Each and every embodiment can be combined unless the context clearly suggests otherwise. Each and every embodiment can be applied to each and every aspect of the invention unless the context clearly suggests otherwise.

[0032] Specific embodiments of the present invention will become evident from the following more detailed description of certain preferred embodiments and the claims.

BRIEF DESCRIPTION OF THE FIGURES

[0033] FIG. **1** shows amino acid sequence alignment of IL-22 from different mammalian species: human (GenBank Accession No. Q9GZX6, SEQ ID NO:4, chimpanzee (GenBank Accession No. XP_003313906, SEQ ID NO:48), orangutan (GenBank Accession No. XP_002823544, SEQ ID NO:49), mouse (GenBank Accession No. Q9JJY9, SEQ ID NO:50) and dog (GenBank Accession No. XP_538274, SEQ ID NO:51).

[0034] FIG. **2** shows mass spectrometry results of the glycosylation status of the Fc region of a typical human monoclonal IgG1 Fc (Panel A), IL-22 IgG1 Fc fusion containing the linker sequence EPKSCDKTHT (SEQ ID NO:33, Panel B), EPKSSDKTHT (SEQ ID NO:40, Panel C), and GGGDKTHT (SEQ ID NO:41, Panel D), and IL-22 IgG4 Fc fusion containing the linker sequence RVESKYGPP without or with the N297G mutation (SEQ ID NO:44, Panels E and F, respectively) and IL-22 IgG1 Fc fusion containing the linker sequence EPKSSDKTHT (SEQ ID NO:40) with the N297G mutation (Panel G).

[0035] FIG. **3** shows sequence alignment of human IL-22 IgG4 Fc fusion (N297G, full length Fc sequence with the C-terminal Lys, SEQ ID NO:16, without Lys SEQ ID NO:8), IL-22 IgG1 Fc fusion (N297G, full length Fc sequence with

the C-terminal Lys, SEQ ID NO:20, without Lys SEQ ID NO:12) and IL-22 (SEQ ID NO:4). The IL-22 sequence shown is the matured form without the leader sequence. The hinge sequence CPPCP (SEQ ID NO:31) is shown in the box, followed by the CH2 and CH3 domains. The N297G substitution and the optional C-terminus Lys residue are marked.

[0036] FIG. **4** presents a graph showing the results of STAT3 luciferase assay. Luciferase activity stimulated by IL-22 IgG4 Fc fusion or IL-22 IgG1 Fc fusion was measured in 293 cells expressing human IL-22R. The results show that IL-22 IgG4 and IL-22 IgG1 Fc fusion exhibited similar in vitro activity.

[0037] FIG. **5** shows the therapeutic effects of mouse IL-22 Fc fusion protein in the dextran sodium sulfate (DSS)-induced mouse IBD model. Mouse IL-22 Fc fusion protein improved colon histology in the DSS-induced IBD mice (FIG. **5**B) and the improvement was translated to reduced colon histology score (FIG. **5**C). IL-22 Fc fusion protein treatment resulted in reduced weight loss of the mice during treatment as compared to dexamethasone, currently the best standard of care in this model (FIG. **5**A).

[0038] FIG. **6** shows the rate of serum clearance of human IL-22 IgG4 and IgG1 Fc fusion proteins in cynomolgus monkeys dosed at 0.15 mg/kg and 1.5 mg/kg on day 0 and day 7.

[0039] FIG. **7** shows the serum levels of three IL-22R downstream genes in cynomolgus monkeys after dosing at 0.15 mg/kg and 1.5 mg/kg at day 1 and day 8 (same dosing regimen as day 0 and day 7 in the FIG. **5**. FIG. **7**A—serum amyloid A (SAA), FIG. **7**B—lipopolysaccharide binding protein (LPS-BP), FIG. **7**C—RegIII/Pancreatitis Associated Protein (PAP or PancrePAP).

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[0040] All publications, patents and patent applications cited herein are hereby expressly incorporated by reference for all purposes.

I. Definitions

[0041] Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, Calif.), and Harlow and Lane (1988) Antibodies: A Laboratory Manual ch. 14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.).

[0042] As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. For example, reference to "an isolated peptide" means one or more isolated peptides.

[0043] The term "IL-22 Fc fusion protein" or "IL-22 fusion protein" as used herein refers to a fusion protein in which IL-22 protein or polypeptide is linked, directly or indirectly, to an IgG Fc region. In certain preferred embodiments, the IL-22 Fc fusion protein of the invention comprises a human IL-22 protein or polypeptide linked to a human IgG Fc region. In certain embodiments, the human IL-22 protein comprises the amino acid sequence of SEQ ID NO:4. However, it is understood that minor sequence variations such as insertions, deletions, substitutions, especially conservative amino acid substitutions of IL-22 or Fc that do not affect the function and/or activity of IL-22 or IL-22 Fc fusion protein are also contemplated by the invention. The IL-22 Fc fusion protein of the invention can bind to IL-22 receptor, which can lead to IL-22 receptor downstream signaling. The functions and/or activities of the IL-22 Fc fusion protein can be assayed by methods known in the art, including without limitation, ELISA, ligand-receptor binding assay and Stat3 luciferase assay. In certain particular embodiments, the Fc region of the IL-22 fusion protein does not possess effector activities (e.g., does not bind to FcγIIIR) or exhibits substantially lower effector activity than a whole IgG antibody. In certain other embodiments, the Fc region of the IL-22 Fc fusion protein does not trigger cytotoxicity such as antibody-dependent cellular cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Unless otherwise specified, "IL-22 fusion protein," "IL-22 Fc fusion," "IL-22 Fc fusion protein" of "IL-22 Fc" are used interchangeably throughout this application.

[0044] The term "IL-22," as used herein, broadly refers to any native IL-22 from any mammalian source, including primates (e.g. humans) and rodents (e.g., mice and rats), unless otherwise indicated. The term encompasses "full-length," unprocessed IL-22 as well as any forms of IL-22 that result from processing in the cell. For example, both full-length IL-22 containing the N-terminal leader sequence and the mature form IL-22 are encompassed by the current invention. The leader sequence (or signal peptide) can be the endogenous IL-22 leader sequence and an exogenous leader sequence of another mammalian secretary protein. The term also encompasses naturally occurring variants of IL-22, e.g., splice variants or allelic variants. The amino acid sequence of an exemplary human IL-22 is shown in SEQ ID NO:4 (mature form, without the signal peptide). Minor sequence variations especially conservative amino acid substitutions of IL-22 that do not affect the IL-22's function and/or activity (e.g., binding to IL-22 receptor) are also contemplated by the invention. FIG. **1** shows an amino acid sequence alignment of IL-22 from several exemplary mammalian species. The asterisks indicate highly conserved amino acid residues across species that are likely important for the functions and/or activities of IL-22. Accordingly, in certain embodiments, the IL-22 Fc fusion protein of the invention comprises an IL-22 polypeptide comprising an amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity to SEQ ID NO:4.

[0045] The term "IL-22 receptor" refers to a heterodimer consisting of IL-22R1 and IL-10R2 or naturally occurring allelic variants thereof. See Ouyang et al., 2011, Annu. Rev. Immunol. 29:159-63. IL-10R2 is ubiquitously expressed by many cell types, and IL-22R1 is expressed only innate cells such as epithelial cells, hepatocytes and keratinocytes.

[0046] The term "Fc region," "Fc domain" or "Fc" refers to a C-terminal non-antigen binding region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native Fc regions and variant Fc regions. In certain embodiments, a human IgG heavy chain Fc region extends from Cys226 to the carboxyl-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present, without affecting the structure or stability of the Fc region. Unless otherwise specified herein, numbering of amino acid

residues in the IgG or Fc region is according to the EU numbering system for antibodies, also called the EU index, as described in Kabat et al., *Sequences of Proteins of Immunological Interest,* 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991.

[0047] In certain embodiments, Fc region refers to an immunoglobulin IgG heavy chain constant region comprising a hinge region (starting at Cys226), an IgG CH2 domain and CH3 domain. The term "hinge region" or "hinge sequence" as used herein refers to the amino acid sequence located between the linker and the CH2 domain. In certain embodiments, the hinge region comprises the amino acid sequence CPPCP (SEQ ID NO:31). In certain embodiments, the hinge region for IL-22 IgG4 Fc fusion protein comprises the CPPCP sequence (SEQ ID NO:31), a sequence found in the native IgG1 hige region, to facilitate dimerization. In certain other embodiments, the Fc region starts at the hinge region and extends to the C-terminus of the IgG heavy chain. In certain particular embodiments, the Fc region comprises the Fc region of human IgG, IgG2, IgG3 or IgG4. In certain particular embodiments, the Fc region comprises the CH2 and CH3 domain of IgG4. In certain other particular embodiments, the Fc region comprises the CH2 and CH3 domain of IgG. As described in the Example section, it was unexpectedly discovered by the applicants that IL-22 IgG4 Fc fusion protein exhibited even superior pharmacokinetic properties than IL-22 IgG1 Fc fusion protein.

[0048] In certain embodiments, the IgG CH2 domain starts at Ala 231. In certain other embodiments, the CH3 domain starts at Gly 341. It is understood that the C-terminus Lys residue of human IgG can be optionally absent. It is also understood that conservative amino acid substitutions of the Fc region without affecting the desired structure and/or stability of Fc is contemplated within the scope of the invention.

[0049] In certain embodiments, the IL-22 is linked to the Fc region via a linker. In certain particular embodiments, the linker is a peptide that connects the C-terminus of IL-22 to the Fc region as described herein. In certain embodiments, native IgG sequences are present in the linker and/or hinge region to minimize and/or avoid the risk of immunogenicity. In other embodiments, minor sequence variations can be introduced to the native sequences to facilitate manufacturing. IL-22 Fc fusion constructs comprising exogenous linker or hinge sequences that exhibit high activity (as measured e.g., by a luciferase assay) are also within the scope of the invention. In certain embodiments, the linker comprises an amino acid sequence that is 8-20 amino acids, 8-16, 8-15, 8-14, 8-13, 8-12, 8-11, 8-10, 8-9, 10-11, 10-12, 10-13, 10-14, 10-15, 10-16, 11-16, 8, 9, 10, 11, 12, 13, 14, 15 or 16 amino acids long. In certain other embodiments, the linker comprises the amino acid sequence DKTHT (SEQ ID NO:32).

[0050] In certain particular embodiments, the linker does not comprise the sequence Gly-Gly-Ser (SEQ ID NO:45), Gly-Gly-Gly-Ser (SEQ ID NO:46) or Gly-Gly-Gly-Gly-Ser (SEQ ID NO:47).

[0051] In certain embodiments, the IL-22 Fc fusion protein comprises an IL-22 polypeptide linked to an Fc region by a linker. The term "linked to" or "fused to" refers to a covalent bond, e.g., a peptide bond, formed between two moieties.

[0052] The term "afucosylation," "afucosylated," "defucosylation," or "defucosylated" refers to the absence or removal of core-fucose from the N-glycan attached to the CH2 domain of Fc.

[0053] It was unexpectedly discovered by the applicants that IL-22 IgG1 Fc fusion proteins, unlike other Fc fusion proteins or antibodies comprising Fc, exhibited high levels (e.g., 30%) of afucosylation in the N-glycans attached to the Fc region. The N-glycans attached to the CH2 domain of Fc is heterogeneous. Antibodies or Fc fusion proteins generated in CHO cells are fucosylated by fucosyltransferase activity. See Shoji-Hosaka et al., J. Biochem. 2006, 140:777-83. Normally, a small percentage of naturally occurring afucosylated IgGs may be detected in human serum. N-glycosylation of the Fc is important for binding to FcγR; and afucosylation of the N-glycan increases Fc's binding capacity to FcγRIIIa. Increased FcγRIIIa binding can enhance antibody-dependent cellular cytotoxicity (ADCC), which can be advantageous in certain antibody therapeutic applications in which cytotoxicity is desirable. See Shoji-Hosaka et al., supra. Such an enhanced effector function, however, can be detrimental when Fc-mediated cytotoxicity is undesirable such as in the case of IL-22 Fc fusion.

[0054] IgG4 Fc is known to exhibit less effector activity than IgG1 Fc. Applicants unexpectedly discovered that IL-22 IgG4 Fc fusion protein also showed high levels of afucosylation in the Fc region. The high-level of afucosylated N-glycan attached to the Fc of IgG4 can increase the undesirable effector activity.

[0055] Thus, in one aspect, the invention provides an IL-22 Fc fusion protein in which the Fc region or CH2 domain is not glycosylated. In certain embodiments, the N-glycosylation site in the CH2 domain is mutated to prevent from glycosylation.

[0056] In certain other embodiments, the glycosylation in the CH2 domain of the Fc region can be eliminated by altering the glycosylation consensus site, i.e., Asn at position 297 followed by any amino acid residue (in the case of human IgG, Ser) and Thr (see FIG. **3**). The glycosylation site can be altered by amino acid insertions, deletions and/or substitutions. For example, one or more amino acid residues can be inserted between Asn and Ser or between Ser and Thr to alter the original glycosylation site, wherein the insertions do not regenerate an N-glycosylation site. In certain particular embodiments, the N297 residue (e.g., the N-glycosylated site in Fc, see FIG. **3**) within the CH2 domain of human IgG Fc is mutated to abolish the glycosylation site. In certain particular embodiments, the N297 residue is changed to Gly, Ala, Gln, Asp or Glu. In some particular embodiments, the N297 residue is changed to Gly or Ala. In other particular embodiments, the N297 residue is changed to Gly. In certain other embodiments, the T299 residue can be substituted with another amino acid, for example Ala, Val or Gly. In certain particular embodiments, the mutations that result in an aglycosylated Fc do not affect the structure and/or stability of the IL-22 Fc fusion protein.

[0057] In a related aspect, the invention provides a method of treating IBD, including UC and CD, methods of inhibiting bacterial infection in the intestine, and methods of improving epithelial integrity, epithelial proliferation, differentiation and/or migration in the intestine, and methods of treating metabolic disorders, type II diabetes, atherosclerosis and diabetic wound healing in a patient in need thereof comprising administering to the patient a pharmaceutical

composition comprising an IL-22 Fc fusion protein wherein the Fc region is not glycosylated.

[0058] In a further aspect, the invention provides a composition comprising IL-22 Fc fusion proteins having low level of or no afucosylation in the Fc region. Specifically, the invention provides a composition comprising IL-22 Fc fusion proteins having an overall afucosylation level in the Fc region of no more than 10%, preferably no more than 5%, more preferably no more than 2%, and most preferably less than 1%. In another aspect, the invention provides methods of treating IBD, including UC and CD, methods of inhibiting bacterial infection in the intestine, and methods of improving epithelial integrity, epithelial proliferation, differentiation and/or migration in the intestine, and methods of treating metabolic disorders, type II diabetes, atherosclerosis, diabetic wound healing, in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising IL-22 Fc fusion proteins having an afucosylation level in the Fc region of no more than 10%, preferably no more than 5%, more preferably no more than 2%, and most preferably less than 1%.

[0059] The term "% afucosylation" refers to the level of afucosylation in the Fc region in a composition of IL-22 Fc fusion proteins. The % afucosylation can be measured by mass spectrometry (MS) and presented as the percentage of afucosylated glycan species (species without the fucose on one Fc domain (minus 1) and on both Fc domains (minus 2) combined) over the entire population of IL-22 Fc fusion proteins. For example, % afucosylation can be calculated as the percentage of the combined area under the minus 1 fucose peak and minus 2 fucose peak over the total area of all glycan species analyzed by MS, such as determined by an Agilent 6520B TOF Mass Spectrometer as described in FIG. **2** and in the examples shown below. The level of afucosylation can be measured by any other suitable methods known in the art, including without limitation HPLC-Chip Cube MS (Agilent) and reverse phase-HPLC. The % afucosylation of IL-22 Fc composition can be used as an indication for determining whether the composition will likely trigger unacceptable level of ADCC, unsuitable for the intended purposes. Accordingly, in certain particular embodiments, the composition comprises IL-22 Fc fusion proteins having an afucosylation level of no more than 10%, preferably no more than 5%, more preferably no more than 3%, and most preferably no more than 1%.

[0060] In certain embodiments, the desired level of afucosylation of an IL-22 Fc composition can be achieved by methods known in the art, including without limitation, by purification. For example, the fucosylated species in a composition can be enriched by affinity chromatography having resins conjugated with a fucose binding moiety, such as an antibody or lectin specific for fucose, especially fucose present in the 1-6 linkage. See e.g., Kobayashi et al, 2012, J. Biol. Chem. 287:33973-82. In certain other embodiments, the fucosylated species can be enriched and separated from afucosylated species using an anti-fucose specific antibody in an affinity column. Alternatively or additionally, afucosylated species can be separated from fucosylated species based on the differential binding affinity to FcγRIIIa using affinity chromatography.

[0061] In certain other advantageous embodiments, the IL-22 Fc fusion protein comprises an Fc region in which the N297 residue in the CH2 domain is mutated. In certain embodiments, the N297 residue is changed to Gly or Ala, preferably to Gly. In certain other embodiments, the N297 residue is deleted. In certain embodiments, the IL-22 Fc fusion protein comprising an Fc having an amino acid substitution at N297 is aglycosylated or not glycosylated. The term "aglycosylated" as used herein refers to a protein or a portion of a protein of interest that is not glycosylated. For example, an IL-22 Fc fusion protein with an aglycosylated Fc region can be made by mutagenizing the N297 residue in the CH2 domain of the Fc region.

[0062] In other embodiments, the N-glycan attached to the wild type N297 residue can be removed enzymatically, e.g., by deglycosylation. Suitable glycolytic enzymes include without limitation, peptide-N-glycosidase (PNGase).

[0063] The term "dimeric IL-22 Fc fusion protein" refers to a dimer in which each monomer comprises an IL-22 Fc fusion protein. The term "monomeric IL-22 Fc fusion protein" refers to a dimer in which one monomer comprises an IL-22 Fc fusion protein (the IL-22 Fc arm), while the other monomer comprises an Fc region without the IL-22 polypeptide (the Fc arm). Accordingly, the dimeric IL-22 Fc fusion protein is bivalent with respect to IL-22R binding, whereas the monomeric IL-22 Fc fusion protein is monovalent with respect to IL-22R binding. The heterodimerization of the monomeric IL-22 Fc fusion protein can be facilitated by methods known in the art, including without limitation, heterodimerization by the knob-into-hole technology. The structure and assembly method of the knob-into-hole technology can be found in, e.g., U.S. Pat. No. 5,821,333, U.S. Pat. No. 7,642,228, US 2011/0287009 and PCT/US2012/059810, hereby incorporated by reference in their entireties. This technology was developed by introducing a "knob" (or a protuberance) by replacing a small amino acid residue with a large one in the CH3 domain of one Fc, and introducing a "hole" (or a cavity) in the CH3 domain of the other Fc by replacing one or more large amino acid residues with smaller ones. In certain embodiments, the IL-22 Fc fusion arm comprises a knob, and the Fc only arm comprises a hole.

[0064] The preferred residues for the formation of a knob are generally naturally occurring amino acid residues and are preferably selected from arginine (R), phenylalanine (F), tyrosine (Y) and tryptophan (W). Most preferred are tryptophan and tyrosine. In one embodiment, the original residue for the formation of the knob has a small side chain volume, such as alanine, asparagine, aspartic acid, glycine, serine, threonine or valine. Exemplary amino acid substitutions in the CH3 domain for forming the knob include without limitation the T366W, T366Y or F405W substitution.

[0065] The preferred residues for the formation of a hole are usually naturally occurring amino acid residues and are preferably selected from alanine (A), serine (S), threonine (T) and valine (V). In one embodiment, the original residue for the formation of the hole has a large side chain volume, such as tyrosine, arginine, phenylalanine or tryptophan. Exemplary amino acid substitutions in the CH3 domain for generating the hole include without limitation the T366S, L368A, F405A, Y407A, Y407T and Y407V substitutions. In certain embodiments, the knob comprises T366W substitution, and the hole comprises the T366S/L368A/Y407V substitutions. In certain particular embodiments, the Fc region of the monomeric IL-22 Fc fusion protein comprises an IgG1 Fc region. In certain particular embodiments, the monomeric IL-22 IgG1 Fc fusion comprises an IL-22 Fc knob arm and an Fc hole arm. In certain embodiments, the IL-22 Fc knob arm comprise a T366W substitution (SEQ ID

NO:61), and the Fc hole arm comprises T366S, L368A and Y407V (SEQ ID NO:62). In certain other embodiments, the Fc region of both arms further comprises an N297G or N297A mutation. In certain embodiments, the monomeric IL-22 Fc fusion protein is expressed in *E. coli* cells.

[0066] The term "wound" refers to an injury, especially one in which the skin or another external surface is torn, pierced, cut, or otherwise broken.

[0067] The term "ulcer" is a site of damage to the skin or mucous membrane that is often characterized by the formation of pus, death of tissue, and is frequently accompanied by an inflammatory reaction.

[0068] The term "intestine" or "gut" as used herein broadly encompasses the small intestine and large intestine.

[0069] An "acceptor human framework" for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as defined below. An acceptor human framework "derived from" a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some embodiments, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0070] "Affinity" refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (e.g., a ligand or an antibody) and its binding partner (e.g., a receptor or an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., IL-22 Fc fusion protein and IL-22 receptor). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (Kd). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

[0071] The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g., bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

[0072] An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, $F(ab')_2$; diabodies; linear antibodies; single-chain antibody molecules (e.g. scFv); and multispecific antibodies formed from antibody fragments.

[0073] An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. An exemplary competition assay is provided herein.

[0074] The term "chimeric" antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0075] The "class" of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively.

[0076] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu); chemotherapeutic agents or drugs (e.g., methotrexate, adriamicin, *vinca* alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and the various antitumor or anticancer agents disclosed below.

[0077] "Effector functions" or "effector activities" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g. B cell receptor); and B cell activation. In certain embodiments, the IL-22 Fc fusion protein does not exhibit any effector function or any detectable effector function. In certain other embodiments, the IL-22 Fc fusion protein exhibits substantially reduced effector function, e.g., about 50%, 60%, 70% 80%, or 90% reduced effector function.

[0078] An "effective amount" or "therapeutically effective amount" of an agent, e.g., a pharmaceutical formulation, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0079] A "suboptimal amount" refers to the amount less than the optimal amount of a therapeutic agent typically used for a certain treatment. When two therapeutic agents are given to a subject, either concurrently or sequentially, each therapeutic agent can be given at a suboptimal amount as compared to the treatment when each therapeutic agent is given alone. For example, in certain embodiments, the subject in need of IBD treatment is administered with the pharmaceutical composition comprising the IL-22 Fc fusion protein of the invention and a dexamethasone at a suboptimal amount.

[0080] "Framework" or "FR" refers to variable domain residues other than hypervariable region (HVR) residues. The FR of a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the HVR

and FR sequences generally appear in the following sequence in VH (or VL): FR1-H1(L1)-FR2-H2(L2)-FR3-H3(L3)-FR4.

[0081] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0082] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. The transformed cell includes transiently or stably transformed cell. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein. In certain embodiments, the host cell is transiently transfected with the exogenous nucleic acid. In certain other embodiments, the host cell is stably transfected with the exogenous nucleic acid.

[0083] A "human antibody" is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[0084] A "human consensus framework" is a framework which represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, Fifth Edition, NIH Publication 91-3242, Bethesda Md. (1991), vols. 1-3. In one embodiment, for the VL, the subgroup is subgroup kappa I as in Kabat et al., supra. In one embodiment, for the VH, the subgroup is subgroup III as in Kabat et al., supra.

[0085] A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (e.g., CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody.

[0086] A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, e.g., a non-human antibody, refers to an antibody that has undergone humanization.

[0087] The term "hypervariable region" or "HVR" as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence ("complementarity determining regions" or "CDRs") and/or form structurally defined loops ("hypervariable loops") and/or contain the antigen-contacting residues ("antigen contacts"). Generally, antibodies comprise six HVRs: three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). Exemplary HVRs herein include:

[0088] (a) hypervariable loops occurring at amino acid residues 26-32 (L), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987));

[0089] (b) CDRs occurring at amino acid residues 24-34 (L), 50-56 (L2), 89-97 (L3), 31-35b (H1), 50-65 (H2), and 95-102 (H3) (Kabat et al., *Sequences of Proteins of Immunological Interest,* 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991));

[0090] (c) antigen contacts occurring at amino acid residues 27c-36 (L), 46-55 (L2), 89-96 (L3), 30-35b (H1), 47-58 (H2), and 93-101 (H3) (MacCallum et al. *J. Mol. Biol.* 262: 732-745 (1996)); and

[0091] (d) combinations of (a), (b), and/or (c), including HVR amino acid residues 46-56 (L2), 47-56 (L2), 48-56 (L2), 49-56 (L2), 26-35 (H1), 26-35b (H1), 49-65 (H2), 93-102 (H3), and 94-102 (H3).

[0092] Unless otherwise indicated, HVR residues and other residues in the variable domain (e.g., FR residues) are numbered herein according to Kabat et al., supra.

[0093] An "immunoconjugate" is an antibody or a fragment of an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

[0094] An "individual," "subject" or "patient" is a mammal. Mammals include, but are not limited to, domesticated animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats). In certain embodiments, the individual, subject or patient is a human.

[0095] An "isolated" IL-22 fusion protein is one which has been separated from the environment of a host cell that recombinantly produces the fusion protein. In some embodiments, an IL-22 fusion protein is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (e.g., ion exchange or reverse phase HPLC).

[0096] An "isolated" nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0097] "Isolated nucleic acid encoding IL-22 Fc fusion protein" refers to one or more nucleic acid molecules encoding the IL-22 Fc fusion protein, including such nucleic acid molecule(s) in a single vector or separate vectors, such nucleic acid molecule(s) transiently or stably transfected into a host cell and such nucleic acid molecule(s) present at one or more locations in a host cell.

[0098] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, e.g., containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically

include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0099] A "naked antibody" refers to an antibody that is not conjugated to a heterologous moiety (e.g., a cytotoxic moiety) or radiolabel. The naked antibody may be present in a pharmaceutical formulation.

[0100] "Native antibodies" refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG antibodies are heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light chains and two identical heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3). Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a constant light (CL) domain. The light chain of an antibody may be assigned to one of two types, called kappa (κ) and lambda (λ), based on the amino acid sequence of its constant domain.

[0101] The term "inflammatory bowel disorder," "inflammatory bowel disease" or IBD is used herein in the broadest sense and includes all diseases and pathological conditions the pathogenesis of which involves recurrent inflammation in the intestine, including small intestine and colon. Commonly seen IBD includes ulcerative colitis and Crohn's disease. IBD is not limited to UC and CD. The manifestations of the disease include but not limited to inflammation and a decrease in epithelial integrity in the intestine.

[0102] The term "cardiovascular disease" or "cardiovascular disorder" is used herein in the broadest sense and includes all diseases and pathological conditions the pathogenesis of which involves abnormalities of the blood vessels, such as, for example, atherosclerotic plaque formation (including stable or unstable/vulnerable plaques), atherosclerosis, arteriosclerosis, arteriolosclerosis, and elevated systemic lipopolysaccharide (LPS) exposure. The term additionally includes diseases and pathological conditions that benefit from the inhibition of the formation of atherosclerotic plaques. Cardiovascular diseases include, without limitation, coronary artery atherosclerosis, coronary microvascular disease, stroke, carotid artery disease, peripheral arterial disease, ischemia, coronary artery disease (CAD), acute coronary syndrome (ACS), coronary heart disease (CHD), conditions associated with CAD and CHD, cerebrovascular disease, peripheral vascular disease, aneurysm, vasculitis, venous thrombosis, diabetes mellitus, and metabolic syndromechronic kidney disease, remote tissue injury after ischemia and reperfusion, cardiopulmonary bypass. Specifically included within this group are all cardiovascular diseases associated with the occurrence, development, or progression of which can be controlled by the inhibition of the atherosclerostic plaque formation.

[0103] The term "cardiovascular condition" is used herein in the broadest sense and includes all cardiovascular conditions and diseases the pathology of which involves atherosclerotic plaque formation (including stable or unstable/vulnerable plaques), atherosclerosis, arteriosclerosis, arteriolosclerosis, and elevated systemic lipopolysaccharide (LPS) exposure. Specifically included within this group are all cardiovascular conditions and diseases associated with the atherosclerotic plaque formation, the occurrence, development, or progression of which can be controlled by the inhibition of the atherosclerotic plaque formation. The term specifically includes diseases and pathological conditions that benefit from the inhibition of the formation of atherosclerotic plaques. Cardiovascular conditions include, without limitation, coronary artery atherosclerosis, coronary microvascular disease, stroke, carotid artery disease, peripheral arterial disease, ischemia, coronary artery disease (CAD), coronary heart disease (CHD), conditions associated with CAD and CHD, cerebrovascular disease and conditions associated with cerebrovascular disease, peripheral vascular disease and conditions associated with peripheral vascular disease, aneurysm, vasculitis, venous thrombosis, diabetes mellitus, and metabolic syndromechronic kidney disease, remote tissue injury after ischemia and reperfusion, and cardiopulmonary bypass. "Conditions associated with cerebrovascular disease" as used herein include, for example, transient ischemic attack (TIA) and stroke. "Conditions associated with peripheral vascular disease" as used herein include, for example, claudication. Specifically included within this group are all cardiovascular diseases and conditions associated with the occurrence, development, or progression of which can be controlled by the inhibition of the atherosclerostic plaque formation.

[0104] Atherosclerotic plaque formation can occur as a result of an innate immune response to metabolic endotoxemia, which is characterized by elevated levels of systemic lipopolysaccharides (LPS) that originate from gut microbiota and a loss of functional integrity in the gut mucosal barrier. The innate immune response to endotoxemia results in the low-grade chronic inflammation that is responsible for plaque formation.

[0105] The term "metabolic syndrome" is used herein in the broadest sense. Metabolic syndrome includes the co-occurrence in an adult subject of several metabolic risk factors, including at least three of the following five traits: abdominal obesity, which can be, for example, a waist circumference in men of greater than or equal to 90 cm and in women greater than or equal to 80 cm; elevated serum triglycerides, which can be, for example, greater than or equal to 150 mg/dL, or drug treatment for elevated triglycerides; reduced serum HDL cholesterol level, which can be, for example, below 40 mg/dL in men and below 50 mg/dL in women, or drug treatment for low HDL cholesterol; hypertension, which can be, for example, systolic blood pressure greater than 130 mmHg and diastolic blood pressure greater than 85 mmHg, or drug treatment for hypertension; and elevated fasting plasma glucose, which can be, for example, greater than or equal to 100 mg/dL, drug treatment for elevated glucose, or previously diagnosed type 2 diabetes. See also Meigs, the Metabolic Syndrome (Insulin

Resistance Syndrome or Syndrome X), http://www.uptodate.com/contents/the-metabolic-syndrome-insulin-resistance-syndrome-or-syndrome-x, the disclosure of which is hereby incorporated by reference herein.

[0106] The term "insulin-related disorder" encompasses diseases or conditions characterized by impaired glucose tolerance. In one embodiment, the insulin-related disorder is diabetes mellitus including, without limitation, Type I (insulin-dependent diabetes mellitus or IDDM), Type II (non-insulin dependent diabetes mellitus or NIDDM) diabetes, gestational diabetes, and any other disorder that would be benefited by agents that stimulate insulin secretion. In another embodiment, the insulin-related disorder is characterized by insulin resistance.

[0107] The term "sepsis" is used in its broadest sense and can encompass a systemic inflammatory state caused by severe infection. Sepsis can caused by the immune system's response to a serious infection, most commonly bacteria, but also fungi, viruses, and parasites in the blood, urinary tract, lungs, skin, or other tissues.

[0108] The term "acute endotoxemia" is used in its broadest sense and can encompass the condition of increased plasma bacterial lipopolysaccharide (LPS). Acute endotoxemia in turn could result in sepsis. Increased LPS in systemic circulation will induce low grade chronic inflammation, activating the endogenous protective host response to elevate plasma lipids, that, in the chronic condition contributes to diet induced obesity, insulin resistance and atherosclerosis, and eventual CVD events.

[0109] As used herein, "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antibodies of the invention are used to delay development of a disease or to slow the progression of a disease.

[0110] For example, with regard to IBD, "treatment" can refer to a decrease in the likelihood of developing IBD, a decrease in the rate of developing IBD and a decrease in the severity of the disease. As another example, with regard to atherosclerotic plaque formation, "treatment" can refer to a decrease in the likelihood of developing atherosclerotic plaque deposits, a decrease in the rate of development of deposits, a decrease in the number or size of existing deposits, or improved plaque stability. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviating symptoms, diminishing any direct or indirect pathological consequences of the disease, preventing the disease, decreasing the rate of disease progression, ameliorating or palliating the disease state, and causing remission or improved prognosis.

[0111] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0112] "Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, Calif., or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0113] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0114] The term "pharmaceutical formulation" or "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[0115] A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharma-

ceutically acceptable carrier includes, but is not limited to, a buffer, excipient, diluent, stabilizer, or preservative.

[0116] The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (See, e.g., Kindt et al. *Kuby Immunology,* 6^{th} ed., W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. See, e.g., Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., Nature 352:624-628 (1991).

[0117] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

II. Compositions and Methods

[0118] In one aspect, the invention is based, in part, on compositions comprising therapeutics that ameliorate IL-22 associated diseases or disorders by increasing IL-22 activities or signaling. In certain embodiments, IL-22 Fc fusion proteins that bind to and activate IL-22 receptor are provided. IL-22 Fc fusion proteins of the invention are useful, e.g., for the diagnosis or treatment of IL-22 associated diseases such as inflammatory bowel disease and wound healing.

[0119] A. Exemplary IL-22 Fusion Protein

[0120] In one aspect, the invention provides isolated IL-22 fusion protein. In certain embodiments, the IL-22 fusion protein binds to and induces IL-22 receptor activity or signaling and/or is an agonist of IL-22 receptor activity.

[0121] In another aspect, an IL-22 Fc fusion protein comprises a polypeptide having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO:4. In other embodiments, the IL-22 Fc fusion protein comprises a polypeptide having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity contains substitutions (e.g., conservative substitutions), insertions, or deletions relative to the reference sequence, but an IL-22 Fc fusion protein comprising that sequence retains the ability to bind to IL-22 receptor. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NOs:8, 10, 12, 14, 24 or 26. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the IL22 (i.e., in the Fc). In certain particular embodiments, the C-terminus Lys residue of Fc is deleted. In certain other embodiments, the C-terminus Gly and Lys residues of Fc are both deleted.

[0122] In certain embodiments, IL-22 Fc fusion proteins variants having one or more amino acid substitutions are provided. Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions." More substantial changes are provided in Table 1 under the heading of "exemplary substitutions," and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into the IL-22 Fc fusion protein and the products screened for a desired activity, e.g., retained/improved IL-22 receptor binding, decreased immunogenicity, or improved IL-22 receptor signaling.

TABLE 1

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

Amino acids may be grouped according to common side-chain properties:

[0123] (1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

[0124] (2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

[0125] (3) acidic: Asp, Glu;

[0126] (4) basic: His, Lys, Arg;

[0127] (5) residues that influence chain orientation: Gly, Pro;

[0128] (6) aromatic: Trp, Tyr, Phe.

[0129] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[0130] A useful method for identification of residues or regions of a protein that may be targeted for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells (1989) *Science,* 244:1081-1085. In this method, a residue or group of target residues (e.g., charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to determine whether the interaction of the protein with its binding partner is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of a protein complex (e.g., a cytokine-receptor complex) can be used to identify contact points between the a protein and its binding partner. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[0131] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one

residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues.

[0132] a) Glycosylation Variants

[0133] In certain embodiments, an Fc fusion protein provided herein is altered to increase or decrease the extent to which the fusion protein, especially the Fc portion of the fusion protein, is glycosylated. Addition or deletion of glycosylation sites to a protein may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0134] Where the fusion protein comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al. *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody or the Fc region of an antibody may be made in order to create Fc variants with certain improved properties.

[0135] The amount of fucose attached to the CH2 domain of the Fc region can be determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 or N297 (e.g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (EU numbering of Fc region residues); however, Asn297 may also be located about ±3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. See, e.g., US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to "defucosylated" or "fucose-deficient" antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki et al. *J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. *Arch. Biochem. Biophys.* 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams et al., especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (see, e.g., Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004); Kanda, Y. et al., *Biotechnol. Bioeng.,* 94(4):680-688 (2006); and WO2003/085107).

[0136] Antibodies variants are further provided with bisected oligosaccharides, e.g., in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, e.g., in WO 2003/011878 (Jean-Mairet et al.); U.S. Pat. No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana et al.). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, e.g., in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

[0137] b) Fe Region Variants

[0138] In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of an Fc fusion protein provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (e.g. a substitution) at one or more amino acid positions.

[0139] In certain embodiments, the invention contemplates an Fc variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half life of the antibody or a fusion protein comprising an Fc region in vivo is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. In vitro and/or in vivo cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody or Fc lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of in vitro assays to assess ADCC activity of a molecule of interest is described in U.S. Pat. No. 5,500,362 (see, e.g. Hellstrom, I. et al. *Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I et al., *Proc. Nat'l Acad. Sci. USA* 82:1499-1502 (1985); U.S. Pat. No. 5,821,337 (see Bruggemann, M. et al., *J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTI® non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, Calif.; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, Wis.). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in a animal model such as that disclosed in Clynes et al. *Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody or Fc is unable to bind C1q and hence lacks CDC activity. See, e.g., C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro et al., *J. Immunol. Methods* 202:163 (1996); Cragg, M. S. et al., *Blood* 101:1045-1052 (2003); and Cragg, M. S. and M. J. Glennie, *Blood* 103:2738-2743 (2004)). FcRn binding and in vivo clearance/half life determinations can also be performed using methods known in the art (see, e.g., Petkova, S. B. et al., *Int'l. Immunol.* 18(12):1759-1769 (2006)).

[0140] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues

238, 265, 269, 270, 297, 327 and 329 (U.S. Pat. No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (U.S. Pat. No. 7,332,581).

[0141] Certain antibody or Fc variants with improved or diminished binding to FcRs are described. (See, e.g., U.S. Pat. No. 6,737,056; WO 2004/056312, and Shields et al., *J. Biol. Chem.* 9(2): 6591-6604 (2001).)

[0142] In certain embodiments, an IL-22 Fc fusion protein comprises an Fc variant with one or more amino acid substitutions which reduce ADCC, e.g., substitution at position 297 of the Fc region to remove the N-glycosylation site and yet retain FcRn binding activity (EU numbering of residues).

[0143] In some embodiments, alterations are made in the Fc region that result in diminished C1q binding and/or Complement Dependent Cytotoxicity (CDC), e.g., as described in U.S. Pat. No. 6,194,551, WO 99/51642, and Idusogie et al. *J. Immunol.* 164: 4178-4184 (2000).

[0144] Antibodies with increased half lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976) and Kim et al., *J. Immunol.* 24:249 (1994)), are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, e.g., substitution of Fc region residue 434 (U.S. Pat. No. 7,371,826).

[0145] See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Pat. No. 5,648,260; U.S. Pat. No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

[0146] c) Cysteine Engineered Variants

[0147] In certain embodiments, it may be desirable to create cysteine engineered Fc fusion protein, in which one or more residues of the Fc region of an antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at accessible sites of the Fc. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the Fc and may be used to conjugate the Fc to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. For example, S400 (EU numbering) of the heavy chain Fc region can be substituted with Cysteine. See e.g., U.S. Pat. No. 7,521,541.

[0148] B. Recombinant Methods and Compositions

[0149] IL-22 Fc fusion proteins may be produced using recombinant methods and compositions, as described in, e.g., *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press) and *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, Calif.). In one embodiment, isolated nucleic acid encoding IL-22 Fc fusion proteins described herein is provided. In a further embodiment, one or more vectors (e.g., expression vectors) comprising such nucleic acid are provided. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (e.g., has been transformed with) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the IL-22 Fc fusion protein. In certain embodiment, the vector is an expression vector. In one embodiment, the host cell is eukaryotic, e.g. a Chinese Hamster Ovary (CHO) cell or lymphoid cell (e.g., Y0, NS0, Sp20 cell). In one embodiment, a method of making an IL-22 Fc fusion protein is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the IL-22 Fc fusion protein, as provided above, under conditions suitable for expression of the Fc fusion protein, and optionally recovering the Fc fusion protein from the host cell (or host cell culture medium).

[0150] For recombinant production of an IL-22 Fc fusion protein, nucleic acid encoding an Fc fusion protein, e.g., as described herein, is isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the fusion protein).

[0151] Suitable host cells for cloning or expression of target protein-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, IL-22 fusion protein may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed or are detrimental. For expression of polypeptides in bacteria, see, e.g., U.S. Pat. Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J., 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the Fc fusion protein may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[0152] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[0153] Suitable host cells for the expression of glycosylated proteins are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[0154] Plant cell cultures can also be utilized as hosts. See, e.g., U.S. Pat. Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[0155] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, e.g., in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, e.g., in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung

cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, e.g., in Mather et al., *Annals N.Y. Acad. Sci.* 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR-CHO cells (Urlaub et al., Proc. Natl. Acad. Sci. USA 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, e.g., Yazaki and Wu, *Methods in Molecular Biology*, Vol. 248 (B.K.C. Lo, ed., Humana Press, Totowa, N.J.), pp. 255-268 (2003).

[0156] C. Assays IL-22 Fc fusion protein provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

[0157] 1. Binding Assays and Other Assays

[0158] In one aspect, an IL-22 Fc fusion protein of the invention is tested for its receptor binding activity, e.g., by known methods such as ELISA, western blotting analysis, cell surfact binding by Scatchard, surface plasmon resonance. In another aspect, competition assays may be used to identify an antibody that competes with the IL-22 Fc fusion protein for binding to the IL-22 receptor. In a further aspect, an IL-22 Fc fusion protein of the invention can be used for detecting the presence or amount of IL-22 receptor or IL22-Binding Protein (soluble receptor) present in a biological sample. In a further aspect, an IL-22 Fc fusion protein of the invention can be used for detecting the presence or amount of IL-22 receptor present in a biological sample. In certain embodiments, the biological sample is first blocked with a non-specific isotype control antibody to saturate any Fc receptors in the sample.

[0159] 2. Activity Assays

[0160] In one aspect, assays are provided for identifying biological activity of IL-22 Fc fusion protein. Biological activity may include, e.g., binding to IL-22 receptor, stimulating IL-22 signaling, and inducing STAT3, RegIII and/or PancrePAP expression.

[0161] D. Conjugates

[0162] The invention also provides conjugates comprising an IL-22 Fc fusion protein described herein conjugated to one or more agents for detection, formulation, half-life extension, mitigating immunogenicity or tissue penetration. Exemplary conjugation includes without limitation PEGylation and attaching to radioactive isotopes.

[0163] In another embodiment, a conjugate comprises an IL-22 Fc fusion protein as described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples include At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu. When the radioconjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example tc99m or I123, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[0164] E. Methods and Compositions for Detection

[0165] In certain embodiments, any of the IL-22 Fc fusion provided herein is useful for detecting the presence of IL-22 receptor in a biological sample. In certain embodiments, the method further comprises the step of blocking any Fc receptors in the sample with a non-specific isotype control antibody. The term "detecting" as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises a cell or tissue, such as epithelial tissues.

[0166] In one embodiment, an IL-22 Fc fusion protein for use in a method of detection is provided. In a further aspect, a method of detecting the presence of IL-22 receptor in a biological sample is provided. In certain embodiments, the method comprises contacting the biological sample with an IL-22 Fc fusion protein as described herein under conditions permissive for binding of the IL-22 Fc fusion protein to IL-22 receptor, and detecting whether a complex is formed between the IL-22 Fc fusion protein and IL-22 receptor. In certain embodiments, the method further comprises the step of blocking any Fc receptors in the sample with a non-specific isotype control antibody. Such method may be an in vitro or in vivo method. In one embodiment, an IL-22 Fc fusion protein is used to select subjects eligible for therapy with IL-22 Fc fusion protein, e.g. where IL-22 receptor is a biomarker for selection of patients.

[0167] In certain embodiments, labeled IL-22 Fc fusion proteins are provided. Labels include, but are not limited to, labels or moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, e.g., through an enzymatic reaction or molecular interaction. Exemplary labels include, but are not limited to, the radioisotopes ^{32}P, ^{14}C, ^{125}I, ^{3}H, and ^{131}I, fluorophores such as rare earth chelates or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, luceriferases, e.g., firefly luciferase and bacterial luciferase (U.S. Pat. No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, horseradish peroxidase (HRP), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases, e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, heterocyclic oxidases such as uricase and xanthine oxidase, coupled with an enzyme that employs hydrogen peroxide to oxidize a dye precursor such as HRP, lactoperoxidase, or microperoxidase, biotin/avidin, spin labels, bacteriophage labels, stable free radicals, and the like.

[0168] F. Pharmaceutical Formulations

[0169] Pharmaceutical formulations of an IL-22 Fc fusion protein as described herein are prepared by mixing such fusion protein having the desired degree of purity with one or more optional pharmaceutically acceptable carriers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbo-

hydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary pharmaceutically acceptable carriers herein further include insterstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[0170] Exemplary lyophilized formulations are described in U.S. Pat. No. 6,267,958. Aqueous formulations include those described in U.S. Pat. No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

[0171] The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide a steroid, TNF antagonist or other anti-inflammatory therapeutics. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

[0172] Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

[0173] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the IL-22 Fc fusion protein, which matrices are in the form of shaped articles, e.g. films, or microcapsules.

[0174] A pharmaceutical composition for topical administration can be formulated, for example, in the form of a topical gel. See e.g., U.S. Pat. No. 5,192,734 (Genentech). In certain embodiments, the composition can be formulated in the presence of cellulose derivatives. In certain other embodiments, the topical formulation can be reconstituted from lyophilized formulation with sufficient buffer or diluent before administration. In certain embodiments, the IL-22 Fc fusion protein is formulated for topical administration to a subject having a defect in epithelial wound healing. In certain particular embodiments, the epithelial wound healing occurs in the skin. In certain other particular embodiments, the subject is a human having a defect in wound healing. In certain other embodiments, the topical formulation comprising an IL-22 Fc fusion protein of the invention can be used to improve wound healing after internal or external surgical incisions.

[0175] The formulations to be used for in vivo administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

[0176] G. Therapeutic Methods and Compositions

[0177] Any of the IL-22 Fc fusion protein provided herein may be used in therapeutic methods. In one aspect, an IL-22 Fc fusion protein for use as a medicament is provided. In further aspects, an IL-22 Fc fusion protein for use in treating IBD, including UC or CD, is provided. In certain embodiments, an IL-22 Fc fusion protein for use in a method of treatment is provided. In certain embodiments, the invention provides an IL-22 Fc fusion protein for use in a method of treating an individual having UC or CD comprising administering to the individual an effective amount of the IL-22 Fc fusion protein. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, e.g., as described below. In further embodiments, the invention provides an IL-22 Fc fusion protein for use in enhancing epithelial proliferation, differentiation and/or migration. In certain particular embodiments, the epithelial tissue is intestinal epithelial tissue. In certain embodiments, the invention provides an IL-22 Fc fusion protein for use in a method of enhancing epithelial proliferation, differentiation and/or migration in an individual comprising administering to the individual an effective amount of the IL-22 Fc fusion protein to enhance epithelial proliferation, differentiation and/or migration. In yet other embodiments, the invention provides an IL-22 Fc fusion protein for use in treating diabetes, especially type II diabetes, diabetic wound healing, metabolic syndromes and atherosclerosis. In certain embodiments, the invention provides an IL-22 Fc fusion protein for use in a method of treating diabetes, especially type II diabetes, diabetic wound healing, metabolic syndromes and atherosclerosis in an individual comprising administering to the individual an effective amount of the IL-22 Fc fusion protein. See Genentech applications Docket numbers PR5586, application Ser. No. 61/800,795, entitled "Using an IL-22 polypeptide for wound healing," and PR5590, application Ser. No. 61/801,144, entitled "Methods of treating cardiovascular conditions and metabolic syndrome using an IL-22 polypeptide," both filed on Mar. 15, 2013. The disclosures of both of the applications are incorporated herein by reference in their entireties. An "individual" according to any of the above embodiments is preferably a human.

[0178] In a further aspect, the invention provides for the use of an IL-22 Fc fusion protein in the manufacture or preparation of a medicament. In one embodiment, the medicament is for treatment of IBD and wound healing. In a further embodiment, the medicament is for use in a method of treating IBD and wound healing comprising administering to an individual having IBD an effective amount of the medicament. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, e.g., as described below. In a further embodiment, the medicament is for suppressing inflammatory response in the gut epithelial cells. In a further embodiment, the medicament is for use in a method of enhancing epithelial proliferation, differentiation and/or migration in an individual comprising administering to the individual an amount effective of the medicament to enhance epithelial proliferation, differentiation and/or migration. An "individual" according to any of the above embodiments may be a human.

[0179] In a further aspect, the invention provides a method for treating IBD, including UC and CD. In one embodiment, the method comprises administering to an individual having

IBD an effective amount of an IL-22 Fc fusion protein. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. An "individual" according to any of the above embodiments may be a human.

[0180] In a further aspect, the invention provides a method for enhancing epithelial proliferation, differentiation and/or migration in an individual. In one embodiment, the method comprises administering to the individual an effective amount of an IL-22 Fc fusion protein to enhance epithelial proliferation, differentiation and/or migration. In one embodiment, an "individual" is a human.

[0181] In a further aspect, the invention provides pharmaceutical formulations comprising any of the IL-22 Fc fusion protein provided herein, e.g., for use in any of the above therapeutic methods. In one embodiment, a pharmaceutical formulation comprises any of the IL-22 Fc fusion proteins provided herein and a pharmaceutically acceptable carrier. In another embodiment, a pharmaceutical formulation comprises any of the IL-22 Fc fusion proteins provided herein and at least one additional therapeutic agent, e.g., as described below.

[0182] IL-22 Fc fusion protein of the invention can be used either alone or in combination with other agents in a therapy. For instance, an aIL-22 Fc fusion protein of the invention may be co-administered with at least one additional therapeutic agent. In certain embodiments, an additional therapeutic agent is an immune suppressant that reduces the inflammatory response including without limitation methotrexate, TNF inhibitor, TNF antagonist, mesalazine, steroid, dexamethasone, and azathioprine, and combination thereof.

[0183] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of the IL-22 Fc fusion protein of the invention can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent or agents. In one embodiment, administration of the IL-22 Fc fusion protein and administration of an additional therapeutic agent occur within about one month, or within about one, two or three weeks, or within about one, two, three, four, five, or six days, of each other.

[0184] An IL-22 Fc fusion protein of the invention (and any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, topical and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g. by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

[0185] IL-22 Fc fusion protein of the invention would be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The IL-22 Fc fusion protein need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of the fusion protein present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[0186] For the prevention or treatment of disease, the appropriate dosage of an IL-22 Fc fusion protein of the invention (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the type of Fc region, the severity and course of the disease, whether the fusion protein is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the IL-22 Fc fusion protein, and the discretion of the attending physician. The IL-22 Fc fusion protein is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 μg/kg to 15 mg/kg (e.g. 0.1 mg/kg-10 mg/kg) or about 0.1 μg/kg to 1.5 mg/kg (e.g., 0.01 mg/kg-1 mg/kg) of the IL-22 Fc fusion protein can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 μg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the IL-22 Fc fusion protein would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g. every week or every three weeks (e.g. such that the patient receives from about two to about twenty, or e.g. about six doses of the IL-22 Fc fusion protein). An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

[0187] It is understood that any of the above formulations or therapeutic methods may be carried out using conjugate of the invention in place of or in addition to an IL-22 Fc fusion protein.

[0188] H. Articles of Manufacture

[0189] In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a

sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an IL-22 Fc fusion protein of the invention. The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises an IL-22 Fc fusion protein of the invention; and (b) a second container with a composition contained therein, wherein the composition comprises a further cytotoxic or otherwise therapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0190] It is understood that any of the above articles of manufacture may include a conjugate of the invention in place of or in addition to an IL-22 Fc fusion protein.

EXAMPLES

[0191] The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided above, and the examples are not intended to limit the scope of the claims.

Example 1 Cloning, Expression and Purification of the IL-22 Fc Fusion Protein

[0192] General molecular cloning and protein purification techniques can be applied in the following experiments.

[0193] i. Cloning

[0194] Full-length human IL-22 was cloned from a human colon cDNA library (Genentech).

[0195] Constructs expressing human IgG1 or IgG4 IL-22Fc fusion protein were generated for this experiment using overlapping PCR technique using the following primers: IL-22 Fc fusion IgG1 forward primer:

(SEQ ID NO: 52)
TTGAATTCCACCATGGGATGGTCATGTATCATCCTTTTTCTAGTA

GCAACTGCAACTGGAGTACATTCAGCGCCCATCAGCTCCCACTGC

AGGC,

[0196] IL-22 Fc fusion IgG1 reverse primer AGGTCGACTCATTTACCCGGAGACAGGGAGAGG (SEQ ID NO:53), IL-22 Fc fusion IgG4 forward primer:

(SEQ ID NO: 54)
TTGAATTCCACCATGGGATGGTCATGTATCATCCTTTTTCTAGTA

GCAACTGCAACTGGAGTACATTCAGCGCCCATCAGCTCCCACTGC

AGGC,

[0197] IL-22 Fc fusion IgG4 reverse primer: AGGTCGACTTATTTACCCAGAGACAGGGAGAGG (SEQ ID NO:55). The PCR products were cloned into expression vectors pRK5.sm (Genentech). The leader sequence (or signal peptide) was cleaved in the cell and the mature IL-22 Fc fusion did not contain the leader sequence. The clones carrying artificial linkers were cloned with primers containing the linker sequences. The N297G mutation was further introduced by mutagenesis PCR using the following primers: IgG1 N297G forward primer: GCG GGA GGA GCA GTA CGG AAG CAC GTA CCG TGT GG (SEQ ID NO:56), IgG1 N297G reverse primer: CCA CAC GGT ACG TGC TTC CGT ACT GCT CCT CCC GC (SEQ ID NO:57), IgG4 N297G forward primer: ACA AAG CCG CGG GAG GAG CAG TTC GGA AGC ACG TAC CGT GTG GTC AGC GTC (SEQ ID NO:58), and IgG4 N297G reverse primer: GAC GCT GAC CAC ACG GTA CGT GCT TCC GAA CTG CTC CTC CCG CGG CTT TGT (SEQ ID NO:59). Sequences of all IL-22Fc constructs were confirmed by DNA sequencing.

[0198] ii. Cell Culture

[0199] CHO cells were grown in suspension by splitting the culture 2 times per week to 0.3×10^6 cells/ml in an incubator set to 37° C. and 5% CO_2.

[0200] iii. Transfection of IL-22 Fc Fusion Protein into CHO Cells and Protein Expression

[0201] CHO cells were seeded at 1.23×10^6 cells/ml in 720 mL culture media. The transfection complex (1.6 mL PEI+ 800 ug DNA in 80 mL serum free media) was incubated for 10 min before added to the cells. The culture was incubated at 33° C., 5% CO_2 for 24 hours. After further culturing for 14 days, the supernatant of the culture was harvested via centrifugation. Transient CHO conditioned media (supernatant from above) was purified using the MabSelect Sure (GE Healthcare) protein A affinity column. The eluate at low pH was neutralized to pH5.0 and further purified through a gel filtration column (GE Healthcare). The eluted peak was pooled, formulated and sterile filtered. The glycosylation status of the Fc region of the fusion protein was analyzed by Mass Spectrometry as discussed below.

[0202] iv. Establishment of Stable Clones Expressing IL-22 Fc Fusion Protein

[0203] The plasmid encoding IL-22 Fc fusion protein was introduced into CHO cells by transfection using Lipofectamine 2000 CD (Invitrogen). After transfection, the cells were centrifuged and re-plated into serum-free selective medium. Isolates were selected for secretion of IL-22 Fc. Clones with the highest titer, as identified by ELISA, were then pooled and scaled for production.

[0204] v. Expression of IL-22 Fc Fusion Protein in *E. coli*

[0205] *E. coli* fermentation feedstock was homogenized and conditioned to 0.4% w/w PEI pH 6.7 and centrifuged. Centrate was purified using a MabSelect Sure (GE Healthcare) protein A affinity column. The eluate at low pH was neutralized to pH 5.0 and further purified through an ion exchange chromatography. Fractions were pooled, formulated and sterile filtered.

Example 2 IL-22 Fc Fusion Protein Exhibited High Percentage of Afucosylation in the Fc Region

[0206] In this study, the glycosylation status of the Fc portion of the IL-22 Fc fusion proteins was examined. Samples of purified IL-22 Fc fusion proteins from transiently transfected cells were digested with trypsin (1:25

trypsin: IL-22 Fc, w/w) for 2 hrs at 37° C. Samples were acidified with trifluoroacetic acid to a final concentration of 0.1% and injected onto a heated C18 column (PLRP-S, 1000A 8 um, Agilent) equilibrated with 0.05% TFA in water. The digestion products were separated by a linear acetonitrile gradient (5 to 60%) over 20 min time. The column was directly connected to the electrospray orifice of an Agilent 6520B TOF Mass Spectrometer and the masses of the eluted fractions were determined in positive ion mode. Since the Fc portions of these fusion constructs are stable in trypsin under these digestion conditions, a direct comparison of the carbohydrate status of various IL-22 fusions could be made.

[0207] As shown in FIG. **2**, both IL-22 IgG1 and IgG4 Fc fusion proteins showed abnormally high levels of afucosylation. The expected masses for a glycosylated Fc of a typical monoclonal IgG1 antibody would be those labeled as 53296, 53458 and 53620 Da of panel A in FIG. **2**. Typically the core carbohydrate species on each arm of the Fc would each consist of the following carbohydrate composition: 4 N-acetyl glucosamine, 3 manose and 1 fucose sugar species (as on the peak labeled 53296 in Panel A). The addition of one or two galactose sugars would produce the peaks labeled 53458 and 53620 Da, respectively (Panel A). A negligible amount of molecules containing sugar moieties that was missing fucose on one arm of the Fc was detected ("−1 fucose").

[0208] Surprisingly, human IL-22 IgG1 Fc fusion proteins of different constructs in which the CH2 domain is glycosylated all exhibited high level of afucosylation, including sugar moieties missing fucose on one arm ("−1 fucose") and both arms of Fc ("−2 fucose"). See FIG. **2**, Panels B-D. These afucosylated molecules comprised as high as about 30% of the total species observed. Afucosylation can increase the undesirable effector activities of the IL-22 IgG1 Fc fusion.

[0209] IgG4 is known to have less effector function as compared to IgG. Unexpectedly, results of Mass Spectrometry analysis also showed the "−1 fucose" and "−2 fucose" glycosylated species in the trypsin-digested Fc regions of human IL-22 IgG4 Fc fusion protein. These afucosylated molecules comprised more than 50% of the total species observed. FIG. **2**, Panel E. Afucosylated antibodies have much enhanced ADCC or CDC cytotoxicity activities, a property not desirable with these IL-22 Fc fusion proteins.

[0210] Subsequently, two additional IL-22 Fc molecules, one containing IgG1 Fc and the other IgG4 Fc were constructed in which the residue in the Fc that would normally be glycosylated (N297) was mutated to a glycine (N297G) thereby preventing attachment of the normal core sugar.

[0211] These were shown to be devoid of any sugar on their Fc portions and both had their expected Fc molecular weights based on their amino acid sequences (FIG. **2**, Panels F and G).

[0212] In summary, the Fc region of the human IL-22 Fc fusion proteins, either IgG1 or IgG4 Fc fusion, showed high levels of afucosylation, which can result in increased ADCC or CDC activities, a property not desirable for use as IL-22 therapeutics. Thus, the non-glycosylated variants were tested in further studies.

Example 3 IL-22 IgG1 and IgG4 Fc Fusion Protein In Vitro Activity Assay

[0213] IL-22 engages IL-22 receptor complex and activates Jak-Stat signaling pathway. STAT3 activation is a predominant event in IL-22 mediated signaling pathway. In this experiment, the in vitro activities of IL-22 Fc fusion proteins were measured using a luciferase reporter assay. HEK 293 cells were engineered to overexpress human IL-22 receptor complex IL22R1 and IL10R2. On day 1, 1×10^5 293 cells were seeded in 24-well plates in 0.4 ml Dulbecco's modified Eagle Medium (DMEM)+10% Fetal Bovine Serum (FBS). On day 2, cells were transfected with a STAT3-driven luciferase reporter and a *Renilla* luciferase control using Lipofectamine 2000 (Invitrogen) in 0.1 ml reduced serum media (Gibco Poti-MEM with reduced serum reduced by at least 50%). The STAT3 luciferase reporter construct contains STAT3-responsive luciferase reporter construct containing tandem repeats of the sis-inducible element (SIE) and the firefly luciferase reporter gene. On day 3, IL-22 Fc fusion proteins produced by either transient or stable CHO clones were titrated into different concentrations in 0.5 ml media, and added on top of transfected cells. On day 4, media were removed and cells were lysed with 100 ul passive lysis buffer (provided by the Dual-Luciferase Reporter 1000 Assay System). Twenty microliter of cell lysates were transferred into 96-well plate and analyzed with Dual-Luciferase Reporter 1000 Assay System on luminometer (Promega). The EC50 was calculated based on the dose-dependent activity in GraphPad Prism software (La Jolla, Calif.). The EC50 values for different IL-22 Fc fusion constructs are shown in Table 2 below.

TABLE 2

IL-22 Fc Constructs	Fc isotype	Linker	Production	EC50 (pM)
1	huIgG1	DKTHT (SEQ ID NO: 32)	CHO	150-200
2	huIgG1	EPKSCDKTHT (SEQ ID NO: 33)	CHO	350-500
3	huIgG1	VEPKSCDKTHT (SEQ ID NO: 34)	CHO	100-150
4	huIgG1	KVEPKSCDKTHT (SEQ ID NO: 35)	CHO	50-75
5	huIgG1	KKVEPKSCDKTHT (SEQ ID NO: 36)	CHO	25-50
6	huIgG1	DKKVEPKSCDKTHT (SEQ ID NO: 37)	CHO	25-50
7	huIgG1	VDKKVEPKSCDKTHT (SEQ ID NO: 38)	CHO	25-50
8	huIgG1	KVDKKVEPKSCDKTHT (SEQ ID NO: 39)	CHO	2.5-5
9	huIgG1	GGGDKTHT (SEQ ID NO: 41)	CHO	50-75
10	huIgG1	GGGSTHT (SEQ ID NO: 63)	CHO	50-100
11	huIgG1	EPKSSDKTHT (SEQ ID NO: 40)	CHO	50-100
12	huIgG1	DKKVEPKSSDKTHT (SEQ ID NO: 64)	CHO	25

TABLE 2-continued

IL-22 Fc Con-structs	Fc isotype	Linker	Pro-duction	EC50 (pM)
13	huIgG1	KVDKKVEPKSSDKTHT (SEQ ID NO: 65)	CHO	25
14	huIgG1	DKTHT (SEQ ID NO: 32) N297A	CHO	150-200
15	huIgG1	EPKSSDKTHT (SEQ ID NO: 40) N297A	CHO	50-100
16	huIgG1	DKTHT (SEQ ID NO: 32) (N297G)	CHO	150-200
17	huIgG1	EPKSSDKTHT (SEQ ID NO: 40) (N297G)	CHO	50-100
18	huIgG1	KKVEPKSSDKTHT (SEQ ID NO: 66) (N297G)	CHO	20
19	huIgG4	SKYGPP (SEQ ID NO: 43)	CHO	150-200
20	huIgG4	SKYGPP (SEQ ID NO: 43) N297G	CHO	75-100
21	huIgG4	RVESKYGPP (SEQ ID NO: 44)	CHO	25-50
22	huIgG4	RVESKYGPP (SEQ ID NO: 44) N297G	CHO	50-75
23	huIgG1	ELKTPLGDTTHT (SEQ ID NO: 42) (IgG3 linker)	CHO	50-75
24	huIgG1	EPKSSDKTHT (SEQ ID NO: 40)	*E. coli*	16
25	huIgG1-monomeric IL-22	EPKSSDKTHT (SEQ ID NO: 40)	*E. coli*	82

[0214] A large number of IL-22 Fc fusion proteins were constructed with linkers of different length and sequences to examine the activities, stability and yield of each design. Linkers with native IgG sequences are preferred to minimize potential risk of immunogenicity; however, linkers with exogenous sequences that showed good in vitro activity were considered and encompassed by the current invention.

[0215] The IL-22 IgG1 Fc fusion protein containing the DKTHT linker (SEQ ID NO:32) was tested in the STAT3 luciferase assay. See Table 2. To improve EC50 of the fusion protein, the linker length was increased from 5 to 10 amino acids containing the native IgG1 sequence EPKSCDKTHT (SEQ ID NO:33). The resulting IL-22 Fc fusion protein, however, exhibited reduced in vitro activity. See Table 2. Surprisingly, an increase in the linker length even by one amino acid VEPKSCDKTHT (SEQ ID NO:34) improved the activity of the IL-22 fusion protein. Further increases in the linker length resulted in further improvement in activity. See Table 2.

[0216] In separate experiments, the Cys in EPKSCDKTHT was changed to Ser to remove the potential of disulfide bond formation. As shown in Table 2, IL-22 Fc fusion with the linker EPKSSDKTHT (SEQ ID NO:40) showed improved activity as compared to the parent linker sequence with the Cys residue. Longer linker sequence incorporating the upstream sequences (into the CH1 domain of IgG1) further improved activity. Constructs with N297G mutation showed similar EC50 values when compared with the wild type counterparts. IL-22 IgG1 (N297G) Fc fusion protein (SEQ ID NO:12) and IL-22 IgG4 (N297G) Fc fusion protein (SEQ ID NO:8) were chosen for further studies.

[0217] The in vitro activities of human IL-22 IgG1 (N297G) Fc fusion protein (SEQ ID NO: 12) or IL-22 IgG4 (N297G) Fc fusion protein (SEQ ID NO:8) expressed from stable clones were tested in the same assay. Data in FIG. **3** show representative results. Both IL-22 IgG1 and IgG4 Fc fusion proteins induced STAT3 activity at a dose-dependent manner. Both IL-22 Fc fusion proteins showed similar potency. IL-22 Fc fusion proteins expressed from transiently transfected cells showed similar results (data not shown). As a control, native IL-22 protein produced in CHO cells was tested in the same assay, and exhibited two to three folds higher potency than the IL-22 Fc fusion proteins.

[0218] In summary, both IgG1 and IgG4 IL-22 Fc fusion proteins exhibited in vitro activity demonstrated by STAT3 luciferase assay. Further, IL-22 Fc fusion proteins with linkers of different length and sequences were shown to activate IL-22R mediated luciferase activity.

Example 4 IL-22 Fc Fusion Proteins Reduced Symptoms of DSS-Induced Colitis in Mice

[0219] Dextran Sodium Sulfate (DSS)-induced colitis is a commonly-accepted mouse colitis model. Oral administration of DSS-containing water rapidly damages colon epithelial cells and causes substantial body weight loss and colon epithelial structure disruption characterized by either immunohistochemical (IHC) staining or histology clinical score by pathologist. In this proof of concept study, the effect of IL-22 Fc fusion protein on DSS-induced colitis was tested.

[0220] In C57BL/6 mice, colitis was induced with drinking water containing 3.5% DSS for five consecutive days starting from day 0. Mouse IL-22 IgG2a Fc (SEQ ID NO:60), a surrogate for human IL-22 Fc fusion protein was dosed through intraperitoneal route at 5 mg/Kg on day −1, 1, 4, and 6. Body weight of the animals was measured daily. On day 8, all animals were sacrificed and colon histology was studied through both IHC staining and manual histological score.

[0221] As shown in FIG. **5**, DSS induced colitis is associated with dramatic body weight loss (FIG. **5**A), colonic epithelial damage and colon inflammation (FIG. **5**B) and high histology score (FIG. **5**C). IL-22Fc treatment significantly prevented weight loss, restored epithelial integrity, diminished inflammation and reduced histology score. See FIG. **5**. The efficacy of IL-22 Fc exceeded the effect of dexamethasone, the steroid standard of care (SOC) that caused significant body weight loss in this study.

Example 5 IL-22 Fc Fusion Protein Pharmacokinetics Study

[0222] The pilot safety and PKPD study in cynomolgus monkeys was approved by the Institutional Animal Care and

Use Committee (IACUC). The study was conducted at Charles River Laboratories (CRL) Preclinical Services (Reno, Nev.). A total of 15 male cynomolgus monkeys (4-5 kg) from CRL stock were randomly assigned to five groups (n=3/group). Animals in group 1 were given an intravenous (i.v.) dose of the control vehicle on Days 1 and 8. Animals in groups 2 and 3 were given a single i.v. bolus dose of IL22-Fc IgG1 at 0.15 and 1.5 mg/kg, respectively, on Days 1 and 8. Animals in groups 4 and 5 were given a single i.v. bolus dose of IL22-Fc IgG4 at 0.15 and 1.5 mg/kg, respectively, on Days 1 and 8. Serum samples were collected at various time points for PK and PD analysis out to Day 43 and concentrations of IL22-Fc were assessed by ELISA.

[0223] For analysis of human IL-22-Fc in cynomolgus monkey serum, mouse anti-human IL-22 mAb (Genentech) was used as a capture antibody in an ELISA assay. The recombinant IL-22 Fc fusion protein was used to develop a standard curve. Plate-bound IL-22-Fc was detected during a 1 hour incubation with HRP-conjugated anti-human-Fcγ-pan murine mAb (Genentech) diluted to 500 ng/mL in assay buffer. After a final wash, tetramethyl benzidine peroxidase substrate (Moss, Inc., Pasadena, Md.) was added, color was developed for 15 minutes, and the reaction was stopped with 1 M phosphoric acid. The plates were read at 450 nm with a 620 nm reference using a microplate reader. The concentrations of IL-22 Fc fusion were calculated from a four-parameter fit of the IL-22 Fc fusion standard curve.

[0224] For PK data calculations, Study Day 1 was converted to PK Day 0 to indicate the start of dose administration. All time points after the in life dosing day are calculated as Study Day minus 1. The serum concentration data for each animal were analyzed using 2 compartment analysis with WinNonlin®, Version 5.2.1 (Pharsight; Mountain View, Calif.).

[0225] The plasma concentrations of IL22-Fc showed a bi-exponential decline after i.v. dosing (0.15 mg/kg and 1.5 mg/kg) with a short distribution phase and a long terminal elimination phase. See FIG. **6**. The two-compartment model with linear elimination of IL-22 Fc from the central compartment described the pharmacokinetic profiles for both the doses well, suggesting negligible target mediated disposition at these dose ranges.

[0226] The maximum serum concentration (C_{max}) and area-under-serum-concentration-time-curve (AUC) estimated by the two-compartmental analysis were roughly linear and dose-proportional. See Table 3. The dose-proportional kinetics suggested IL-22R saturation at the doses tested. As shown in FIG. **6**, the IL-22 IgG4 Fc fusion unexpectedly showed a 2-fold slower CL and greater than 2-fold higher exposure compared to the IgG1 Fc fusion. Without limiting to particular mechanisms, the faster clearance of IgG1 fusion may be due to less stability of the IgG1 fusion construct because the greater than 2-fold faster CL of the IL-22 IgG1 Fc fusion appeared to be mainly driven by a larger volume of distribution. The Beta half-lives of 4-5 days were similar between IgG1 and IgG4 fusions.

TABLE 3

Group	AUC (day • ug/mL)	C_{max} (ug/mL)	CL (mL/day/kg)	Beta_HL* (day)
0.15 mg/kg IgG1	4.47 ± 0.603	2.70 ± 0.607	34.0 ± 4.26	4.02 ± 0.478
1.5 mg/kg IgG1	51.1 ± 9.70	30.5 ± 4.14	30.1 ± 6.18	5.33 ± 0.580
0.15 mg/kg IgG4	11.3 ± 0.752	3.99 ± 0.432	13.3 ± 0.853	4.61 ± 0.394
1.5 mg/kg IgG4	102 ± 18.9	33.4 ± 4.02	15.0 ± 2.58	5.80 ± 0.770

*Beta half-life

Example 6 Assessment of In Vivo Activity of IL-22Fc in Cynomolgus Monkey

[0227] Cynomolgus monkeys (*Macaca fascicularis*) were dosed intravenously with IL-22 Fc fusion of isotype IgG1 or IgG4 as indicated, at doses of 0.15 mg/kg or 1.5 mg/kg. IL-22 binding to IL-22 receptor triggers the expression of several genes including Serum Amyloid A (SAA), RegIII/Pancreatitis Associated Protein (PAP, also called PancrePAP), and Lipopolysaccharide Binding Protein (LPS-BP). In this study, IL-22 Fc fusion protein in vivo activities were analyzed by measuring the expression of SAA, PancrePAP, and LPS-BP. Serum samples were obtained over a time course pre- and post-dose, as indicated in the graph. Circulating levels of monkey SAA were quantified in serum using a commercial enzyme-linked immunosorbent assay (ELISA) kit (catalog #3400-2) available from Life Diagnostics (West Chester, Pa.). Circulating levels of RegII/PAP were quantified in serum using a commercial ELISA kit (catalog PancrePAP) produced by Dynabio (Marseille, France).

[0228] Levels of Lipoprotein Binding Protein (LBP) in serum samples were determined by using a qualified ELISA. Biotinylated-Lipoprotein (Enzo Life Sciences, Farmingdale, N.Y.) was coated on a Streptavidin coated microtiter plate (Thermo; Rockland, Ill.). Recombinant human LBP (R&D Systems, Inc., Minneapolis, Minn.) was used as a standard in the assays. Bound LBP analyte was detected with an anti-LBP mouse monoclonal antibody (Thermo, Rockland, Ill.). Horseradish peroxidase (HRP)-conjugated $F(ab')_2$ fragment goat anti-mouse IgG, Fc (Jackson ImmunoResearch, West Grove, Pa.) was used for detection. The colorimetric signals were visualized after addition of 3,3',5,5'-tetramethylbenzidine (TMB) substrate (Kirkegaard & Perry Laboratories, Gaithersburg, Md.). The reaction was stopped by addition of 1 M phosphoric acid and absorbance was measured at 450 nm using 650 nm as reference on a plate reader (Molecular Devices, Sunnyvale, Calif.). All ELISA samples were run according to manufacturer's specifications and were prepared either at a single dilution in duplicate or at four serial dilutions in singlicate and concentrations were interpolated from a standard curve. The mean value of each sample was reported.

[0229] As shown in FIG. **7**, SAA, LPS-BP, and RegIII/PAP serum protein levels were induced by IL-22Fc in vivo. Dose-dependent responses were observed in vivo in non-human primates, indicating IL-22R engagement and suggesting saturation by IL-22Fc. In the majority of cases, no increase in the serum protein levels was observed 24 hours after the second dose, suggesting that serum SAA, LPS-BP, and RegIII/PAP proteins had reached the maximal levels. Serum levels of all three proteins declined slowly over the 35-day recovery period, returning to baseline in most animals. The exception being the RegII/PAP levels in the IgG4

high dose group, which appeared to stay elevated throughout the 42-day course. This may reflect improved PK and increased exposure by AUC for the IL-22 IgG4 Fc fusion protein as compared to IL-22 IgG1 Fc fusion protein.

Example 7 Miscellaneous Examples

[0230] In data not shown herein, applicants have internal data (described but not shown here) that indicate that IL-22 polypeptides (including IL-22 polypeptides comprising a CH2 and CH3 domain) generally are useful for improving or accelerating diabetic wound healing, treating atherosclerosis, treating cardiovascular diseases wherein the patient has atherosclerotic plaques, treating metabolic syndrome, treating mild and acute endotoxemia, treating sepsis and treating insulin-related disorders. Applicants believe that the IL-22 Fc fusion proteins of this invention will also be effective in these diseases and disorders.

[0231] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

SEQUENCE LISTING

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cgcaccttca tgctggctaa ggaggctagc ttggctgata acaacacaga cgttcgtctc 180

attggggaga aactgttcca cggagtcagt atgagtgagc gctgctatct gatgaagcag 240

gtgctgaact tcacccttga agaagtgctg ttccctcaat ctgataggtt ccagccttat 300

atgcaggagg tggtgccctt cctggccagg ctcagcaaca ggctaagcac atgtcatatt 360

gaaggtgatg acctgcatat ccagaggaat gtgcaaaagc tgaaggacac agtgaaaaag 420

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Human IL-22 (Full)

<400> SEQUENCE: 2

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1 5 10 15

Val His Ser Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn
20 25 30

Phe Gln Gln Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu
35 40 45

Ala Ser Leu Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys
50 55 60

Leu Phe His Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln
65 70 75 80

Val Leu Asn Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg
85 90 95

Phe Gln Pro Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser
100 105 110

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Asn Arg Leu Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln
        115                 120                 125

Arg Asn Val Gln Lys Leu Lys Asp Thr Val Lys Lys Leu Gly Glu Ser
    130                 135                 140

Gly Glu Ile Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu
145                 150                 155                 160

Arg Asn Ala Cys Ile
                165
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<220> FEATURE:
<223> OTHER INFORMATION: IL-22 DNA (mature, without the leader sequence)

<400> SEQUENCE: 3

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ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag    180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct    240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat    300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa    360

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```

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1               5                   10                  15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
            20                  25                  30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
        35                  40                  45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
    50                  55                  60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
                85                  90                  95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
            100                 105                 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140
```

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Cys Ile
145

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<220> FEATURE:
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<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 leader sequence

<400> SEQUENCE: 6

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Val His Ser

<210> SEQ ID NO 7
<211> LENGTH: 1128
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (minus C-terminal Lys) N297G

<400> SEQUENCE: 7

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ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag 180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct 240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat 300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa 360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct 420

ctgagaaatg cctgcattcg cgttgagtcc aaatatggtc ccccatgccc accatgccca 480

gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact 540

ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac 600

cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag 660

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tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta 1020

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<210> SEQ ID NO 8
<211> LENGTH: 376
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (minus C-terminal Lys) N297G

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Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
100 105 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
130 135 140

Cys Ile Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
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Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
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Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
180 185 190

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
195 200 205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
210 215 220

Gln Phe Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
225 230 235 240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
245 250 255

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
260 265 270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
275 280 285

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
290 295 300

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Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
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Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                325                 330                 335

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
            340                 345                 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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Lys Ser Leu Ser Leu Ser Leu Gly
    370                 375
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<210> SEQ ID NO 9
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (minus C-terminal Lys) N297A

<400> SEQUENCE: 9

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ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag    180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct    240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat    300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa    360

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ctgagaaatg cctgcattcg cgttgagtcc aaatatggtc ccccatgccc accatgccca    480

gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact    540

ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac    600

cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag    660

ccgcgggagg agcagttcgc tagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac    720

caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc    780

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ctgcccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa    900

ggcttctacc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac    960

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta   1020

accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag   1080

gctctgcaca accactacac acagaagagc ctctccctgt ctctgggt                1128
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<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (minus C-terminal Lys)
N297A

<400> SEQUENCE: 10

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Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
100 105 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
130 135 140

Cys Ile Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
145 150 155 160

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
165 170 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
180 185 190

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
195 200 205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
210 215 220

Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
225 230 235 240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
245 250 255

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
260 265 270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
275 280 285

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
290 295 300

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
305 310 315 320

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
325 330 335

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
340 345 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
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Lys Ser Leu Ser Leu Ser Leu Gly

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370 375

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (minus C-terminal Lys) N297G

<400> SEQUENCE: 11

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ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag 180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct 240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat 300

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aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct 420

ctgagaaatg cctgcattga gcccaaatct agtgacaaaa ctcacacatg cccaccgtgc 480

ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac 540

accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa 600

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 660

aagccgcggg aggagcagta cggaagcacg taccgtgtgg tcagcgtcct caccgtcctg 720

caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca 780

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accctgcccc catcccggga gagatgacc aagaaccagg tcagcctgac ctgcctggtc 900

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac 960

aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1020

ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat 1080

gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg t 1131

<210> SEQ ID NO 12
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (minus C-terminal Lys) N297G

<400> SEQUENCE: 12

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Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

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Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
    50                  55                  60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
                85                  90                  95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
            100                 105                 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140

Cys Ile Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
145                 150                 155                 160

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                165                 170                 175

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            180                 185                 190

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        195                 200                 205

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    210                 215                 220

Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
225                 230                 235                 240

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                245                 250                 255

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            260                 265                 270

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
        275                 280                 285

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    290                 295                 300

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
305                 310                 315                 320

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                325                 330                 335

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            340                 345                 350

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
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Gln Lys Ser Leu Ser Leu Ser Pro Gly
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<210> SEQ ID NO 13
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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (minus C-terminal Lys)
      N297A
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ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag 180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct 240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat 300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa 360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct 420

ctgagaaatg cctgcattga gcccaaatct agtgacaaaa ctcacacatg cccaccgtgc 480

ccagcacctg aactcctggg gggaccgtca gtcttcctct tcccccaaa acccaaggac 540

accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa 600

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 660

aagccgcggg aggagcagta cgctagcacg taccgtgtgg tcagcgtcct caccgtcctg 720

caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca 780

gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac 840

accctgcccc catcccggga gagatgacc aagaaccagg tcagcctgac ctgcctggtc 900

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac 960

aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1020

ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat 1080

gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg t 1131

<210> SEQ ID NO 14
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (minus C-terminal Lys) N297A

<400> SEQUENCE: 14

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1 5 10 15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
100 105 110

Gln Lys Leu Lys Asp Thr Val Lys Lys Leu Gly Glu Ser Gly Glu Ile

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        115                 120                 125

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140

Cys Ile Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
145                 150                 155                 160

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                165                 170                 175

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            180                 185                 190

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        195                 200                 205

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    210                 215                 220

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
225                 230                 235                 240

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                245                 250                 255

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            260                 265                 270

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
        275                 280                 285

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    290                 295                 300

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
305                 310                 315                 320

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                325                 330                 335

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            340                 345                 350

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        355                 360                 365

Gln Lys Ser Leu Ser Leu Ser Pro Gly
    370                 375


<210> SEQ ID NO 15
<211> LENGTH: 1131
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (full) N297G

<400> SEQUENCE: 15

gcgcccatca gctcccactg caggcttgac aagtccaact tccagcagcc ctatatcacc     60

aaccgcacct tcatgctggc taaggaggct agcttggctg ataacaacac agacgttcgt    120

ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag    180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct    240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat    300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa    360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct    420
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ctgagaaatg cctgcattcg cgttgagtcc aaatatggtc ccccatgccc accatgccca    480

gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact    540

ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac    600

cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag    660

ccgcgggagg agcagttcgg aagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac    720

caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc    780

tccatcgaga aaaccatctc caaagccaaa gggcagcccc gagagccaca ggtgtacacc    840

ctgcccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa    900

ggcttctacc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac    960

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta   1020

accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag   1080

gctctgcaca accactacac acagaagagc ctctccctgt ctctgggtaa a            1131
```

<210> SEQ ID NO 16
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (full) N297G

<400> SEQUENCE: 16

```
Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1               5                   10                  15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
            20                  25                  30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
        35                  40                  45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
    50                  55                  60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
                85                  90                  95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
            100                 105                 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140

Cys Ile Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
145                 150                 155                 160

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
                165                 170                 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            180                 185                 190

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
        195                 200                 205
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Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    210                 215                 220

Gln Phe Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
225                 230                 235                 240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                245                 250                 255

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            260                 265                 270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
        275                 280                 285

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    290                 295                 300

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
305                 310                 315                 320

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                325                 330                 335

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
            340                 345                 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        355                 360                 365

Lys Ser Leu Ser Leu Ser Leu Gly Lys
    370                 375


<210> SEQ ID NO 17
<211> LENGTH: 1131
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (full) N297A

<400> SEQUENCE: 17

gcgcccatca gctcccactg caggcttgac aagtccaact tccagcagcc ctatatcacc     60

aaccgcacct tcatgctggc taaggaggct agcttggctg ataacaacac agacgttcgt    120

ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag    180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct    240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat    300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa    360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct    420

ctgagaaatg cctgcattcg cgttgagtcc aaatatggtc ccccatgccc accatgccca    480

gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact    540

ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac    600

cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag    660

ccgcgggagg agcagttcgc tagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac    720

caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc    780

tccatcgaga aaaccatctc caaagccaaa gggcagcccc gagagccaca ggtgtacacc    840

ctgcccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa    900
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ggcttctacc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac 960

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta 1020

accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag 1080

gctctgcaca accactacac acagaagagc ctctccctgt ctctgggtaa a 1131

<210> SEQ ID NO 18
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (full) N297A

<400> SEQUENCE: 18

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1 5 10 15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
100 105 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
130 135 140

Cys Ile Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
145 150 155 160

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
165 170 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
180 185 190

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
195 200 205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
210 215 220

Gln Phe Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
225 230 235 240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
245 250 255

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
260 265 270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
275 280 285

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Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
290 295 300

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
305 310 315 320

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
325 330 335

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
340 345 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
355 360 365

Lys Ser Leu Ser Leu Ser Leu Gly Lys
370 375

<210> SEQ ID NO 19
<211> LENGTH: 1134
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (full) N297G

<400> SEQUENCE: 19

gcgcccatca gctcccactg caggcttgac aagtccaact tccagcagcc ctatatcacc 60

aaccgcacct tcatgctggc taaggaggct agcttggctg ataacaacac agacgttcgt 120

ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag 180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct 240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat 300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa 360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct 420

ctgagaaatg cctgcattga gcccaaatct agtgacaaaa ctcacacatg cccaccgtgc 480

ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac 540

accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa 600

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 660

aagccgcggg aggagcagta cggaagcacg taccgtgtgg tcagcgtcct caccgtcctg 720

caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca 780

gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac 840

accctgcccc catcccggga agagatgacc aagaaccagg tcagcctgac ctgcctggtc 900

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac 960

aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1020

ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat 1080

gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaa 1134

<210> SEQ ID NO 20
<211> LENGTH: 378
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

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polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (full) N297G

<400> SEQUENCE: 20

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1 5 10 15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
100 105 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
130 135 140

Cys Ile Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
145 150 155 160

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
165 170 175

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
180 185 190

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
195 200 205

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
210 215 220

Glu Gln Tyr Gly Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
225 230 235 240

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
245 250 255

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
260 265 270

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
275 280 285

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
290 295 300

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
305 310 315 320

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
325 330 335

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
340 345 350

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
355 360 365

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

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370 375

<210> SEQ ID NO 21
<211> LENGTH: 1134
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (full) N297A

<400> SEQUENCE: 21

gcgcccatca gctcccactg caggcttgac aagtccaact tccagcagcc ctatatcacc 60

aaccgcacct tcatgctggc taaggaggct agcttggctg ataacaacac agacgttcgt 120

ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag 180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct 240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat 300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa 360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct 420

ctgagaaatg cctgcattga gcccaaatct agtgacaaaa ctcacacatg cccaccgtgc 480

ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac 540

accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa 600

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca 660

aagccgcggg aggagcagta cgctagcacg taccgtgtgg tcagcgtcct caccgtcctg 720

caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca 780

gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac 840

accctgcccc catcccggga gagatgacc aagaaccagg tcagcctgac ctgcctggtc 900

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac 960

aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag 1020

ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat 1080

gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaa 1134

<210> SEQ ID NO 22
<211> LENGTH: 378
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (full) N297A

<400> SEQUENCE: 22

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1 5 10 15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn

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    50                  55                  60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
                85                  90                  95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
            100                 105                 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140

Cys Ile Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
145                 150                 155                 160

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                165                 170                 175

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            180                 185                 190

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        195                 200                 205

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    210                 215                 220

Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
225                 230                 235                 240

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                245                 250                 255

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            260                 265                 270

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
        275                 280                 285

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    290                 295                 300

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
305                 310                 315                 320

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                325                 330                 335

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            340                 345                 350

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        355                 360                 365

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    370                 375


<210> SEQ ID NO 23
<211> LENGTH: 1128
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (wt N297, minus Lys)

<400> SEQUENCE: 23

gcgcccatca gctcccactg caggcttgac aagtccaact tccagcagcc ctatatcacc     60
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aaccgcacct tcatgctggc taaggaggct agcttggctg ataacaacac agacgttcgt    120

ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag    180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct    240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat    300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa    360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct    420

ctgagaaatg cctgcattcg cgttgagtcc aaatatggtc ccccatgccc accatgccca    480

gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact    540

ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac    600

cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag    660

ccgcgggagg agcagttcaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac    720

caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc    780

tccatcgaga aaaccatctc caaagccaaa gggcagcccc gagagccaca ggtgtacacc    840

ctgcccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa    900

ggcttctacc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac    960

tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta   1020

accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag   1080

gctctgcaca accactacac acagaagagc ctctccctgt ctctgggt                1128
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<210> SEQ ID NO 24
<211> LENGTH: 376
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (wt N297, minus Lys)

<400> SEQUENCE: 24

```
Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1               5                   10                  15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
            20                  25                  30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
        35                  40                  45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
    50                  55                  60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
                85                  90                  95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
            100                 105                 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140
```

-continued

```
Cys Ile Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
145                 150                 155                 160

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
                165                 170                 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            180                 185                 190

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
        195                 200                 205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    210                 215                 220

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
225                 230                 235                 240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                245                 250                 255

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            260                 265                 270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
        275                 280                 285

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    290                 295                 300

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
305                 310                 315                 320

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                325                 330                 335

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
            340                 345                 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        355                 360                 365

Lys Ser Leu Ser Leu Ser Leu Gly
    370                 375


<210> SEQ ID NO 25
<211> LENGTH: 1131
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (wt N297, minus Lys)

<400> SEQUENCE: 25

gcgcccatca gctcccactg caggcttgac aagtccaact tccagcagcc ctatatcacc     60

aaccgcacct tcatgctggc taaggaggct agcttggctg ataacaacac agacgttcgt    120

ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag    180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct    240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat    300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa    360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct    420

ctgagaaatg cctgcattga gcccaaatct agtgacaaaa ctcacacatg cccaccgtgc    480

ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac    540
```

-continued

```
accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa    600

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca    660

aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg    720

caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca    780

gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac    840

accctgcccc catcccggga agagatgacc aagaaccagg tcagcctgac ctgcctggtc    900

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac    960

aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag   1020

ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat   1080

gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg t            1131
```

<210> SEQ ID NO 26
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (wt N297, minus Lys)

<400> SEQUENCE: 26

```
Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1               5                   10                  15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
            20                  25                  30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
        35                  40                  45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
    50                  55                  60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
                85                  90                  95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
            100                 105                 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140

Cys Ile Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
145                 150                 155                 160

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
                165                 170                 175

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
            180                 185                 190

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
        195                 200                 205

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
    210                 215                 220
```

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```
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
225                 230                 235                 240

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
                245                 250                 255

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
            260                 265                 270

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
        275                 280                 285

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
    290                 295                 300

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
305                 310                 315                 320

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
                325                 330                 335

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
            340                 345                 350

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
        355                 360                 365

Gln Lys Ser Leu Ser Leu Ser Pro Gly
    370                 375


<210> SEQ ID NO 27
<211> LENGTH: 1131
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (N297 wt, add Lys to
      C-terminus)

<400> SEQUENCE: 27

gcgcccatca gctcccactg caggcttgac aagtccaact tccagcagcc ctatatcacc     60

aaccgcacct tcatgctggc taaggaggct agcttggctg ataacaacac agacgttcgt    120

ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag    180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct    240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat    300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa    360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct    420

ctgagaaatg cctgcattcg cgttgagtcc aaatatggtc ccccatgccc accatgccca    480

gcacctgagt tcctgggggg accatcagtc ttcctgttcc ccccaaaacc caaggacact    540

ctcatgatct cccggacccc tgaggtcacg tgcgtggtgg tggacgtgag ccaggaagac    600

cccgaggtcc agttcaactg gtacgtggat ggcgtggagg tgcataatgc caagacaaag    660

ccgcgggagg agcagttcaa cagcacgtac cgtgtggtca gcgtcctcac cgtcctgcac    720

caggactggc tgaacggcaa ggagtacaag tgcaaggtct ccaacaaagg cctcccgtcc    780

tccatcgaga aaaccatctc caaagccaaa gggcagcccc gagagccaca ggtgtacacc    840

ctgcccccat cccaggagga gatgaccaag aaccaggtca gcctgacctg cctggtcaaa    900

ggcttctacc ccagcgacat cgccgtggag tgggagagca atgggcagcc ggagaacaac    960
```

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tacaagacca cgcctcccgt gctggactcc gacggctcct tcttcctcta cagcaggcta 1020

accgtggaca agagcaggtg gcaggagggg aatgtcttct catgctccgt gatgcatgag 1080

gctctgcaca accactacac acagaagagc ctctccctgt ctctgggtaa a 1131

<210> SEQ ID NO 28
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG4 (N297 wt, add Lys to C-terminus)

<400> SEQUENCE: 28

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1 5 10 15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
100 105 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
130 135 140

Cys Ile Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
145 150 155 160

Ala Pro Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
165 170 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
180 185 190

Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
195 200 205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
210 215 220

Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
225 230 235 240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
245 250 255

Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
260 265 270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met
275 280 285

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
290 295 300

-continued

```
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
305                 310                 315                 320

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                325                 330                 335

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val
            340                 345                 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        355                 360                 365

Lys Ser Leu Ser Leu Ser Leu Gly Lys
    370                 375
```

<210> SEQ ID NO 29
<211> LENGTH: 1134
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (N297 wt, add Lys to C-terminus)

<400> SEQUENCE: 29

```
gcgcccatca gctcccactg caggcttgac aagtccaact tccagcagcc ctatatcacc     60

aaccgcacct tcatgctggc taaggaggct agcttggctg ataacaacac agacgttcgt    120

ctcattgggg agaaactgtt ccacggagtc agtatgagtg agcgctgcta tctgatgaag    180

caggtgctga acttcaccct tgaagaagtg ctgttccctc aatctgatag gttccagcct    240

tatatgcagg aggtggtgcc cttcctggcc aggctcagca acaggctaag cacatgtcat    300

attgaaggtg atgacctgca tatccagagg aatgtgcaaa agctgaagga cacagtgaaa    360

aagcttggag agagtggaga gatcaaagca attggagaac tggatttgct gtttatgtct    420

ctgagaaatg cctgcattga gcccaaatct agtgacaaaa ctcacacatg cccaccgtgc    480

ccagcacctg aactcctggg gggaccgtca gtcttcctct tccccccaaa acccaaggac    540

accctcatga tctcccggac ccctgaggtc acatgcgtgg tggtggacgt gagccacgaa    600

gaccctgagg tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca    660

aagccgcggg aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg    720

caccaggact ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca    780

gcccccatcg agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac    840

accctgcccc catcccggga agagatgacc aagaaccagg tcagcctgac ctgcctggtc    900

aaaggcttct atcccagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac    960

aactacaaga ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag   1020

ctcaccgtgg acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat   1080

gaggctctgc acaaccacta cacgcagaag agcctctccc tgtctccggg taaa         1134
```

<210> SEQ ID NO 30
<211> LENGTH: 378
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

-continued

<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG1 (N297 wt, add Lys to C-terminus)

<400> SEQUENCE: 30

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1 5 10 15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
100 105 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
130 135 140

Cys Ile Glu Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys
145 150 155 160

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
165 170 175

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
180 185 190

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
195 200 205

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
210 215 220

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
225 230 235 240

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
245 250 255

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
260 265 270

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
275 280 285

Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
290 295 300

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
305 310 315 320

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
325 330 335

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
340 345 350

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
355 360 365

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys

-continued

370 375

<210> SEQ ID NO 31
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic hinge peptide

<400> SEQUENCE: 31

Cys Pro Pro Cys Pro
1 5

<210> SEQ ID NO 32
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 32

Asp Lys Thr His Thr
1 5

<210> SEQ ID NO 33
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 33

Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 34
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 34

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 35
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 35

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 36
<211> LENGTH: 13
<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 36

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 37
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 37

Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 38
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 38

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10 15

<210> SEQ ID NO 39
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 39

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
1 5 10 15

<210> SEQ ID NO 40
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 40

Glu Pro Lys Ser Ser Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 41
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 41

-continued

Gly Gly Gly Asp Lys Thr His Thr
1 5

<210> SEQ ID NO 42
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker (IgG3) peptide

<400> SEQUENCE: 42

Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr
1 5 10

<210> SEQ ID NO 43
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 43

Ser Lys Tyr Gly Pro Pro
1 5

<210> SEQ ID NO 44
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 44

Arg Val Glu Ser Lys Tyr Gly Pro Pro
1 5

<210> SEQ ID NO 45
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 45

Gly Gly Ser
1

<210> SEQ ID NO 46
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 46

Gly Gly Gly Ser
1

<210> SEQ ID NO 47

-continued

<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 47

Gly Gly Gly Gly Ser
1 5

<210> SEQ ID NO 48
<211> LENGTH: 146
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 48

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Ser Phe Gln Gln
1 5 10 15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
100 105 110

Gln Lys Leu Lys Asp Thr Val Lys Lys Leu Gly Glu Asn Gly Glu Ile
115 120 125

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
130 135 140

Cys Ile
145

<210> SEQ ID NO 49
<211> LENGTH: 146
<212> TYPE: PRT
<213> ORGANISM: Pongo abelii

<400> SEQUENCE: 49

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1 5 10 15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
20 25 30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe Arg
35 40 45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
50 55 60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65 70 75 80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
85 90 95

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```
Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
            100                 105                 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140

Cys Ile
145


<210> SEQ ID NO 50
<211> LENGTH: 146
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 50

Leu Pro Val Asn Thr Arg Cys Lys Leu Glu Val Ser Asn Phe Gln Gln
1               5                   10                  15

Pro Tyr Ile Val Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
            20                  25                  30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe Arg
        35                  40                  45

Gly Val Ser Ala Lys Asp Gln Cys Tyr Leu Met Lys Gln Val Leu Asn
    50                  55                  60

Phe Thr Leu Glu Asp Val Leu Leu Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Thr Lys Leu Ser Asn Gln Leu
                85                  90                  95

Ser Ser Cys His Ile Ser Gly Asp Asp Gln Asn Ile Gln Lys Asn Val
            100                 105                 110

Arg Arg Leu Lys Glu Thr Val Lys Lys Leu Gly Glu Ser Gly Glu Ile
        115                 120                 125

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140

Cys Val
145


<210> SEQ ID NO 51
<211> LENGTH: 146
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 51

Leu Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1               5                   10                  15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
            20                  25                  30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
        35                  40                  45

Gly Val Asn Met Gly Glu Arg Cys Tyr Leu Met Lys Glu Val Leu Asn
    50                  55                  60

Phe Thr Leu Glu Glu Val Leu Leu Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Lys Leu
                85                  90                  95
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Ser Gln Cys His Ile Glu Asn Asp Asp Gln His Ile Gln Arg Asn Val
100 105 110

Gln Lys Leu Lys Asp Thr Val Gln Lys Leu Gly Glu Asn Gly Glu Ile
115 120 125

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ala Leu Arg Asn Ala
130 135 140

Cys Val
145

<210> SEQ ID NO 52
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic IL-22 Fc fusion protein IgG1 forward primer

<400> SEQUENCE: 52

ttgaattcca ccatgggatg gtcatgtatc atcctttttc tagtagcaac tgcaactgga 60

gtacattcag cgcccatcag ctcccactgc aggc 94

<210> SEQ ID NO 53
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic IL-22 Fc fusion IgG1 reverse primer

<400> SEQUENCE: 53

aggtcgactc atttacccgg agacagggag agg 33

<210> SEQ ID NO 54
<211> LENGTH: 94
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic IL-22 Fc fusion IgG4 forward primer

<400> SEQUENCE: 54

ttgaattcca ccatgggatg gtcatgtatc atcctttttc tagtagcaac tgcaactgga 60

gtacattcag cgcccatcag ctcccactgc aggc 94

<210> SEQ ID NO 55
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic IL-22 Fc fusion IgG4 reverse primer

<400> SEQUENCE: 55

aggtcgactt atttacccag agacagggag agg 33

<210> SEQ ID NO 56
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic IgG1 N297G forward primer

-continued

<400> SEQUENCE: 56

gcgggaggag cagtacggaa gcacgtaccg tgtgg 35

<210> SEQ ID NO 57
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic IgG1 N297G reverse primer

<400> SEQUENCE: 57

ccacacggta cgtgcttccg tactgctcct cccgc 35

<210> SEQ ID NO 58
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic IgG4 N297G forward primer

<400> SEQUENCE: 58

acaaagccgc gggaggagca gttcggaagc acgtaccgtg tggtcagcgt c 51

<210> SEQ ID NO 59
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic IgG4 N297G reverse primer

<400> SEQUENCE: 59

gacgctgacc acacggtacg tgcttccgaa ctgctcctcc cgcggctttg t 51

<210> SEQ ID NO 60
<211> LENGTH: 411
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 Fc fusion IgG2a

<400> SEQUENCE: 60

Met Ala Val Leu Gln Lys Ser Met Ser Phe Ser Leu Met Gly Thr Leu
1 5 10 15

Ala Ala Ser Cys Leu Leu Leu Ile Ala Leu Trp Ala Gln Glu Ala Asn
20 25 30

Ala Leu Pro Val Asn Thr Arg Cys Lys Leu Glu Val Ser Asn Phe Gln
35 40 45

Gln Pro Tyr Ile Val Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser
50 55 60

Leu Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe
65 70 75 80

Arg Gly Val Ser Ala Lys Asp Gln Cys Tyr Leu Met Lys Gln Val Leu
85 90 95

Asn Phe Thr Leu Glu Asp Val Leu Leu Pro Gln Ser Asp Arg Phe Gln

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            100                 105                 110

Pro Tyr Met Gln Glu Val Val Pro Phe Leu Thr Lys Leu Ser Asn Gln
        115                 120                 125

Leu Ser Ser Cys His Ile Ser Gly Asp Asp Gln Asn Ile Gln Lys Asn
    130                 135                 140

Val Arg Arg Leu Lys Glu Thr Val Lys Lys Leu Gly Glu Ser Gly Glu
145                 150                 155                 160

Ile Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn
                165                 170                 175

Ala Cys Val Ala Arg Gly Pro Thr Ile Lys Pro Cys Pro Pro Cys Lys
            180                 185                 190

Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro
        195                 200                 205

Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Ile Val Thr
    210                 215                 220

Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser
225                 230                 235                 240

Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His
                245                 250                 255

Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile
            260                 265                 270

Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys Cys Lys Val Asn
        275                 280                 285

Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile Ser Lys Pro Lys
    290                 295                 300

Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Glu Glu
305                 310                 315                 320

Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met Val Thr Asp Phe
                325                 330                 335

Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn Gly Lys Thr Glu
            340                 345                 350

Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser Asp Gly Ser Tyr
        355                 360                 365

Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn Trp Val Glu Arg
    370                 375                 380

Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn His His
385                 390                 395                 400

Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
                405                 410


<210> SEQ ID NO 61
<211> LENGTH: 372
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: IL-22 IgG1 fusion knob (T366W) minus Lys

<400> SEQUENCE: 61

Ala Pro Ile Ser Ser His Cys Arg Leu Asp Lys Ser Asn Phe Gln Gln
1               5                   10                  15

Pro Tyr Ile Thr Asn Arg Thr Phe Met Leu Ala Lys Glu Ala Ser Leu
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-continued

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            20                  25                  30

Ala Asp Asn Asn Thr Asp Val Arg Leu Ile Gly Glu Lys Leu Phe His
        35                  40                  45

Gly Val Ser Met Ser Glu Arg Cys Tyr Leu Met Lys Gln Val Leu Asn
    50                  55                  60

Phe Thr Leu Glu Glu Val Leu Phe Pro Gln Ser Asp Arg Phe Gln Pro
65                  70                  75                  80

Tyr Met Gln Glu Val Val Pro Phe Leu Ala Arg Leu Ser Asn Arg Leu
                85                  90                  95

Ser Thr Cys His Ile Glu Gly Asp Asp Leu His Ile Gln Arg Asn Val
            100                 105                 110

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

Lys Ala Ile Gly Glu Leu Asp Leu Leu Phe Met Ser Leu Arg Asn Ala
    130                 135                 140

Cys Ile Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
145                 150                 155                 160

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                165                 170                 175

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            180                 185                 190

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        195                 200                 205

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    210                 215                 220

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
225                 230                 235                 240

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                245                 250                 255

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            260                 265                 270

Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln
        275                 280                 285

Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    290                 295                 300

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
305                 310                 315                 320

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                325                 330                 335

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            340                 345                 350

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        355                 360                 365

Leu Ser Pro Gly
    370


<210> SEQ ID NO 62
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
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-continued

<220> FEATURE:
<223> OTHER INFORMATION: Monomeric Fc hole

<400> SEQUENCE: 62

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130 135 140

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

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165 170 175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Val Ser Lys Leu Thr Val
180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210 215 220

Pro Gly
225

<210> SEQ ID NO 63
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 63

Gly Gly Gly Ser Thr His Thr
1 5

<210> SEQ ID NO 64
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 64

Asp Lys Lys Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr

-continued

1 5 10

<210> SEQ ID NO 65
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 65

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr
1 5 10 15

<210> SEQ ID NO 66
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 66

Lys Lys Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 67
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 67

Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 68
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 68

Lys Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr
1 5 10

<210> SEQ ID NO 69
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic linker peptide

<400> SEQUENCE: 69

Val Asp Lys Lys Val Glu Pro Lys Ser Ser Asp Lys Thr His Thr
1 5 10 15

What is claimed is:

1. An IL-22 Fc fusion protein that binds to IL-22 receptor, said IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, wherein the IL-22 Fc fusion protein comprises an amino acid sequence having at least 95% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12 and SEQ ID NO:14, and wherein the Fc region is not glycosylated.

2. The IL-22 Fc fusion protein of claim **1**, wherein the amino acid sequence has at least 98% sequence identity.

3. The IL-22 Fc fusion protein of claim **1** or **2**, wherein the amino acid sequence has at least 99% sequence identity.

4. The IL-22 Fc fusion protein of any one of claims **1-3**, wherein the amino acid sequence has at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12.

5. The IL-22 Fc fusion protein of any one of claims **1-4**, wherein the amino acid sequence has at least 99% sequence identity to the amino acid sequence of SEQ ID NO:8.

6. The IL-22 Fc fusion protein of any one of claims **1-5**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12.

7. The IL-22 Fc fusion protein of any one of claims **1-6**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

8. The IL-22 Fc fusion protein of any one of claims **1-7**, wherein the IL-22 Fc fusion protein is produced by the process comprising the step of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein.

9. The IL-22 Fc fusion protein of claim **8**, wherein the process further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium.

10. The IL-22 Fc fusion protein of claim **8** or **9**, wherein the host cell is an *E. coli* cell.

11. The IL-22 Fc fusion protein of claim **8** or **9**, wherein the host cell is a CHO cell.

12. An IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an IgG Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, and wherein the Fc region is not glycosylated.

13. The IL-22 Fc fusion protein of claim **12**, wherein the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31).

14. The IL-22 Fc fusion protein of claim **12** or **13**, wherein in the Fc region the N297 residue is changed and/or the T299 residue is changed.

15. The IL-22 Fc fusion protein of claim **14**, wherein the N297 residue is changed to Gly or Ala.

16. The IL-22 Fc fusion protein of claim **14** or **15**, wherein the N297 residue is changed to Gly.

17. The IL-22 Fc fusion protein of any one of claims **14-16**, wherein the T299 residue is changed to Ala, Gly or Val.

18. The IL-22 Fc fusion protein of any one of claims **12-17**, wherein the linker is 8-20 amino acids long.

19. The IL-22 Fc fusion protein of any one of claims **12-18**, wherein the linker is 8-16 amino acids long.

20. The IL-22 Fc fusion protein of any one of claims **12-19**, wherein the linker is 10-16 amino acids long.

21. The IL-22 Fc fusion protein of any one of claims **12-20**, wherein the Fc region comprises the CH2 and CH3 domain of IgG1.

22. The IL-22 Fc fusion protein of 12-21, wherein the linker comprises the amino acid sequence DKTHT (SEQ ID NO:32).

23. The IL-22 Fc fusion protein of any one of claims **12-22**, wherein the linker is at least 11 amino acids long and comprises the amino acid sequence EPKSCDKTHT (SEQ ID NO: 33).

24. The IL022 Fc fusion protein of any one of claims **12-23**, wherein the linker comprises the amino acid sequence VEPKSCDKTHT (SEQ ID NO:34), KVEPKSCDKTHT (SEQ ID NO:35), KKVEPKSCDKTHT (SEQ ID NO:36), DKKVEPKSCDKTHT (SEQ ID NO:37), VDKKVEPKSCDKTHT (SEQ ID NO:38), or KVDKKVEPKSCDKTHT (SEQ ID NO:39).

25. The IL-22 Fc fusion protein of any one of claims **12-22**, wherein the linker comprises the amino acid sequence EPKSSDKTHT (SEQ ID NO:40).

26. The IL-22 Fc fusion protein of any one of claims **12-22** and **25**, wherein the linker comprises the amino acid sequence VEPKSSDKTHT (SEQ ID NO:67), KVEPKSSDKTHT (SEQ ID NO:68), KKVEPKSSDKTHT (SEQ ID NO:66), DKKVEPKSSDKTHT (SEQ ID NO:64), VDKKVEPKSSDKTHT (SEQ ID NO:69), or KVDKKVEPKSSDKTHT (SEQ ID NO:65).

27. The IL-22 Fc fusion protein of claim **22**, wherein the linker does not comprise the amino acid sequence GGS (SEQ ID NO:45).

28. The IL-22 Fc fusion protein of any one of claims **12-22**, **25**, and **27** comprising the amino acid sequence of SEQ ID NO: 12 or SEQ ID NO: 14.

29. The IL-22 Fc fusion protein of any one of claims **12-22**, **25** and **27-28** comprising the amino acid sequence of SEQ ID NO: 12.

30. The IL-22 Fc fusion protein of any one of claims **12-20**, wherein the Fc region comprises the CH2 and CH3 domain of IgG4.

31. The IL-22 Fc fusion protein of any one of claims **12-20** and **30**, wherein the linker comprises the amino acid sequence SKYGPP (SEQ ID NO:43).

32. The IL-22 Fc fusion protein of any one of claims **12-20** and **30-31**, wherein the linker comprises the amino acid sequence RVESKYGPP (SEQ ID NO:44).

33. The IL-22 Fc fusion protein of any one of claims **12-20**, and **30-32** comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:10.

34. The IL-22 Fc fusion protein of any one of claims **12-20** and **30-33** comprising the amino acid sequence of SEQ ID NO:8.

35. The IL-22 Fc fusion protein of any one of claims **12-34** produced by the method comprising the step of culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein.

36. The IL-22 Fc fusion protein of claim **35**, wherein the method further comprises the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium.

37. The IL-22 Fc fusion protein of claim **35** or **36**, wherein the host cell is a CHO cell.

38. The IL-22 Fc fusion protein of claim **35** or **36**, wherein the host cell is an *E. coli* cell.

39. The IL-22 Fc fusion protein of any one of claims **1-38**, wherein the IL-22 fusion protein is a dimeric IL-22 Fc fusion protein.

40. The IL-22 Fc fusion protein of any one of claims **1-38**, wherein the IL-22 fusion protein is a monomeric IL-22 Fc fusion protein.

41. The IL-22 Fc fusion protein of any one of claims **1-40**, wherein the IL-22 polypeptide comprises the amino acid sequence of SEQ ID NO:4.

42. A monomeric IL-22 Fc fusion protein comprising an IL-22 Fc fusion arm comprising the amino acid sequence of SEQ ID NO:61, and an Fc arm comprising the amino acid sequence of SEQ ID NO:62.

43. The monomeric IL-22 Fc fusion protein of claim **42** produced by the process comprising the step of culturing one or more host cells comprising one or more nucleic acid molecules capable of expressing the IL-22 Fc fusion arm comprising the amino acid sequence of SEQ ID NO:61 and the Fc arm comprising the amino acid sequence of SEQ ID NO:62.

44. The monomeric IL-22 Fc fusion protein of claim **43**, wherein the method further comprises the step of obtaining the monomeric IL-22 Fc fusion protein from the cell culture or culture medium.

45. The monomeric IL-22 Fc fusion protein of claim **42** or **43**, wherein the one or more host cells are *E. coli* cells.

46. The monomeric IL-22 Fc fusion protein of claim **42** or **43**, wherein the one or more host cells are CHO cells.

47. A method of making the monomeric IL-22 Fc fusion protein of any one of claims **42-46**, comprising the step of culturing one or more host cells comprising one or more nucleic acid molecules capable of expressing the IL-22 Fc arm comprising the amino acid sequence of SEQ ID NO:61 and the Fc arm comprising the amino acid sequence of SEQ ID NO:62.

48. The method of claim **47** further comprising the step of obtaining the monomeric IL-22 Fc fusion protein from the cell culture or culture medium.

49. The method of claim **47** or **48**, wherein the one or more host cells are *E. coli* cells.

50. The method of claim **47** or **48**, wherein the one or more host cells are a CHO cells.

51. A composition comprising an IL-22 Fc fusion protein, said IL-22 Fc fusion protein comprising an IL-22 polypeptide linked to an Fc region by a linker, wherein the Fc region comprises a hinge region, an IgG CH2 domain and an IgG CH3 domain, and wherein the composition has an afucosylation level in the CH2 domain of no more than 5%.

52. The composition of claim **51** wherein the afucosylation level is no more than 2%.

53. The composition of claim **51** or **52** wherein the afucosylation level is less than 1%

54. The composition of any one of claims **51-53**, wherein the afucosylation level is measured by mass spectrometry.

55. The composition of any one of claims **51-54**, wherein the Fc region comprises the CH2 and CH3 domain of IgG1 or IgG4.

56. The composition of claim **55**, wherein the Fc region comprises the CH2 and CH3 domain of IgG1.

57. The composition of claim **55**, wherein the Fc region comprises the CH2 and CH3 domain of IgG4.

58. The composition of any one of claims **51-57**, wherein the hinge region comprises the amino acid sequence of CPPCP (SEQ ID NO:31).

59. The composition of any one of claims **51-58**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26.

60. The composition of any one of claims **51-55**, and **57-59**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24.

61. The composition of any one of claims **51-56** and **58-59**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:26.

62. The composition of any one of claims **51-61**, wherein the composition is produced by the process comprising the steps of: culturing a host cell capable of expressing the IL-22 Fc fusion protein under conditions suitable for expression of the IL-22 Fc fusion protein, and obtaining the IL-22 Fc fusion protein from the cell culture or culture medium, wherein the composition has an afucosylation level in the CH2 domain of the Fc region of no more than 5%.

63. The composition of claim **62** wherein the afucosylation level is no more than 2%.

64. The composition of claim **62** or **63** wherein the afucosylation level is less than 1%.

65. The composition of any one of claims **62-64** wherein the IL-22 Fc fusion protein is obtained by purification.

66. The composition of claim **65**, wherein the IL-22 Fc fusion is purified by affinity chromatography.

67. The composition of any one of claims **51-66**, wherein the host cell is a CHO cell.

68. The composition of any one of claims **51-67** wherein the IL-22 polypeptide comprises the amino acid sequence of SEQ ID NO:4.

69. An isolated nucleic acid encoding the IL-22 Fc fusion protein of any one of claims **1-46** and **51-68**.

70. The isolated nucleic acid of claim **69**, wherein the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8, SEQ ID NO: 10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:24 or SEQ ID NO:26.

71. The isolated nucleic acid of claim **69** or **70**, wherein the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO: 12.

72. The isolated nucleic acid of any one of claims **69-71**, wherein the nucleic acid encodes the IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

73. The isolated nucleic acid of any one of claims **69-72** comprising the polynucleotide sequence of SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:23 or SEQ ID NO:25.

74. The isolated nucleic acid of any one of claims **69-73** comprising the polynucleotide sequence of SEQ ID NO:7 or SEQ ID NO: 11.

75. The isolated nucleic acid of any one of claims **69-74** comprising the polynucleotide sequence of SEQ ID NO:7.

76. A vector comprising the nucleic acid of any one of claims **69-75**.

77. A host cell comprising the vector of claim **76**.

78. The host cell of claim **77**, wherein the host cell is a prokaryotic cell or eukaryotic cell.

79. The host cell of claim **77** or **78**, wherein the host cell is a prokaryotic cell.

80. The host cell of claim **78** or **79**, wherein the prokaryotic cell is an *E. coli* cell.

81. The host cell of claim **77** or **78**, wherein the host cell is a eukaryotic cell.

82. The host cell of claim **77** or **81**, wherein the eukaryotic cell is a CHO cell.

83. A method of making an IL-22 Fc fusion protein comprising the step of culturing the host cell of any one of claims **77-83** under conditions suitable for expression of the IL-22 Fc fusion protein.

84. The method of claim **83**, further comprising the step of obtaining the IL-22 Fc fusion protein from the cell culture or culture medium.

85. The method of claim **84**, further comprising the step of removing afucosylated IL-22 Fc fusion protein.

86. The method of claim **85**, wherein the afucosylated IL-22 Fc fusion protein is removed by affinity column chromatography.

87. The method of claim **83** or **84**, wherein the host cell is an *E. coli* cell.

88. The method of any one of claims **83-86**, wherein the host cell is a CHO cell.

89. A composition comprising an IL-22 Fc fusion protein according to any one of claims **1-46** and **51-68**.

90. A composition comprising an IL-22 Fc fusion protein produced by the method of any one of claims **83-88**.

91. A pharmaceutical composition comprising a therapeutically effective amount of the IL-22 Fc fusion protein according to any one of claims **1-46** and **51-68** and at least one pharmaceutically acceptable carrier.

92. The pharmaceutical composition of claim **91**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:24, or SEQ ID NO:26.

93. The pharmaceutical composition of claim **91** or **92** wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12.

94. The pharmaceutical composition of any one of claims **91-93** wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:8.

95. The pharmaceutical composition of any one of claims **91-94**, wherein the IL-22 Fc fusion protein is produced in *E. coli*.

96. The pharmaceutical composition of any one of claims **91-95**, wherein the Fc region of the IL-22 Fc fusion protein is not glycosylated.

97. The pharmaceutical composition of any one of claims **91-96**, wherein the IL-22 Fc fusion protein does not induce antibody dependent cellular cytotoxicity.

98. The pharmaceutical composition of any one of claims **91-97**, further comprising dexamethasone or a TNF antagonist.

99. The pharmaceutical composition of claim **98**, wherein the dexamethasone or a TNF antagonist is present at a suboptimal amount.

100. A method of treating inflammatory bowel disease (IBD) in a subject in need thereof comprising administering to the subject the pharmaceutical composition of any one of claims **91-99**.

101. A method of treating IBD in a patient comprising administering to the subject in need thereof a pharmaceutical composition comprising IL-22 Fc fusion proteins of any one of claims **1-46** or the compositions of any one of claims **51-68**.

102. The method of claim **100** or **101**, wherein the IBD is ulcerative colitis or Crohn's disease.

103. The method of any one of claims **100-102**, wherein the IBD is ulcerative colitis.

104. The method of any one of claims **100-102**, wherein the IBD is Crohn's disease.

105. The method of any one of claims **101-104**, wherein the Fc region of the IL-22 Fc fusion protein is not glycosylated.

106. The method of claim **105**, wherein the N297 residue of the Fc region is changed.

107. The method of claim **106**, wherein the N297 residue of the Fc region is changed to Gly or Ala.

108. The method of claim **106** or **107**, wherein the N297 residue of the Fc region is changed to Gly.

109. The method of any one of claims **101-108**, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14.

110. The method of claim **109**, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12.

111. The method of claim **110**, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

112. The method of any one of claims **100-111**, wherein the IL-22 Fc fusion protein is produced in *E. coli*.

113. The method of any one of claims **100-104**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26.

114. The method of claim **113**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24.

115. The method of claim **113** or **114**, wherein the IL-22 Fc fusion protein is produced in CHO cells.

116. The method of any one of claims **113-115**, wherein the pharmaceutical composition has an afucosylation level in the CH2 domain of the IL-22 Fc fusion protein of no more than 5%.

117. The method of claim **116**, wherein the afucosylation level is no more than 2%.

118. The method of claim **117**, wherein the afucosylation level is less than 1%.

119. The method of any one of claims **100-118**, wherein the subject is a human.

120. A method of inhibiting microbial infection in the intestine of a subject in need thereof comprising the step of administering to the subject the pharmaceutical composition of any one of claims **91-99**.

121. A method of preserving goblet cells in the intestine during a microbial infection in a subject in need thereof comprising administering to the subject the pharmaceutical composition of any one of claims **91-99**.

122. A method of enhancing epithelial cell integrity, epithelial cell proliferation, epithelial cell differentiation, epithelial cell migration or epithelial wound healing in the intestine in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of any one of claims **91-99**.

123. The method of claim **119**, wherein the epithelial cell is intestinal epithelial cell.

124. The method of any one of claims **120-123**, wherein the Fc region of the IL-22 Fc fusion protein is not glycosylated.

125. The method of claim **124**, wherein the N297 residue of the Fc region is changed.

126. The method of claim **125**, wherein the N297 residue of the Fc region is changed to Gly or Ala.

127. The method of claim **124** or **125**, wherein the N297 residue of the Fc region is changed to Gly.

128. The method of any one of claims **120-127**, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, or SEQ ID NO:14.

129. The method of claim **128**, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:12.

130. The method of claim **128** or **129**, wherein the pharmaceutical composition comprises an IL-22 Fc fusion protein comprising the amino acid sequence of SEQ ID NO:8.

131. The method of any one of claims **120-130**, wherein the IL-22 Fc fusion protein is produced in *E. coli*.

132. The method of any one of claims **120-123**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:26.

133. The method of claim **132**, wherein the IL-22 Fc fusion protein comprises the amino acid sequence of SEQ ID NO:24.

134. The method of claim **132** or **133**, wherein the IL-22 Fc fusion protein is produced in CHO cells.

135. The method of any one of claims **132-134**, wherein the pharmaceutical composition has an afucosylation level in the CH2 domain of the IL-22 Fc fusion protein of no more than 5%.

136. The method of claim **135**, wherein the afucosylation level is no more than 2%.

137. The method of claim **136**, wherein the afucosylation level is less than 1%.

138. The method of any one of claims **120-137**, wherein the subject is a human.

139. The method of any one of claims **100-138**, wherein the pharmaceutical composition is administered intravenously, subcutaneously or topically.

140. The method of any one of claims **100-139**, wherein the patient is further administered a suboptimal amount of dexamethasone.

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