US 20150368338A1

(19) **United States**

(12) **Patent Application Publication**

Chi et al.

(10) **Pub. No.: US 2015/0368338 A1**

(43) **Pub. Date: Dec. 24, 2015**

(54) **INTERFERON ALPHA AND OMEGA ANTIBODY ANTAGONISTS**

(71) Applicant: **Janssen Biotech, Inc.**, Horsham, PA (US)

(72) Inventors: **Ellen Chi**, San Diego, CA (US); **Judith Connor**, San Diego, CA (US); **Chichi Huang**, Spring House, PA (US); **Jarrat Jordan**, Spring House, PA (US); **Xiefan Lin-Schmidt**, San Diego, CA (US); **Jinquan Luo**, Spring House, PA (US); **Lu Lu**, Spring House, PA (US); **Christian Martinez**, San Diego, CA (US); **Galina Obmolova**, Spring House, PA (US); **Ronald Swanson**, San Diego, CA (US)

(21) Appl. No.: **14/745,939**

(22) Filed: **Jun. 22, 2015**

Related U.S. Application Data

(60) Provisional application No. 62/015,765, filed on Jun. 23, 2014.

Publication Classification

(51) **Int. Cl.**

C07K 16/24	(2006.01)
A61K 45/06	(2006.01)
A61K 39/395	(2006.01)

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

CPC ***C07K 16/249*** (2013.01); ***A61K 39/3955*** (2013.01); ***A61K 45/06*** (2013.01); *C07K 2317/76* (2013.01); *C07K 2317/92* (2013.01); *C07K 2317/52* (2013.01); *C07K 2317/31* (2013.01); *A61K 2039/505* (2013.01)

(57) **ABSTRACT**

The present invention relates to antibodies that broady neutralize interferon-α and interferon-ω, polynucleotides encoding the antibodies or fragments, and methods of making and using the foregoing.

Figure 1A

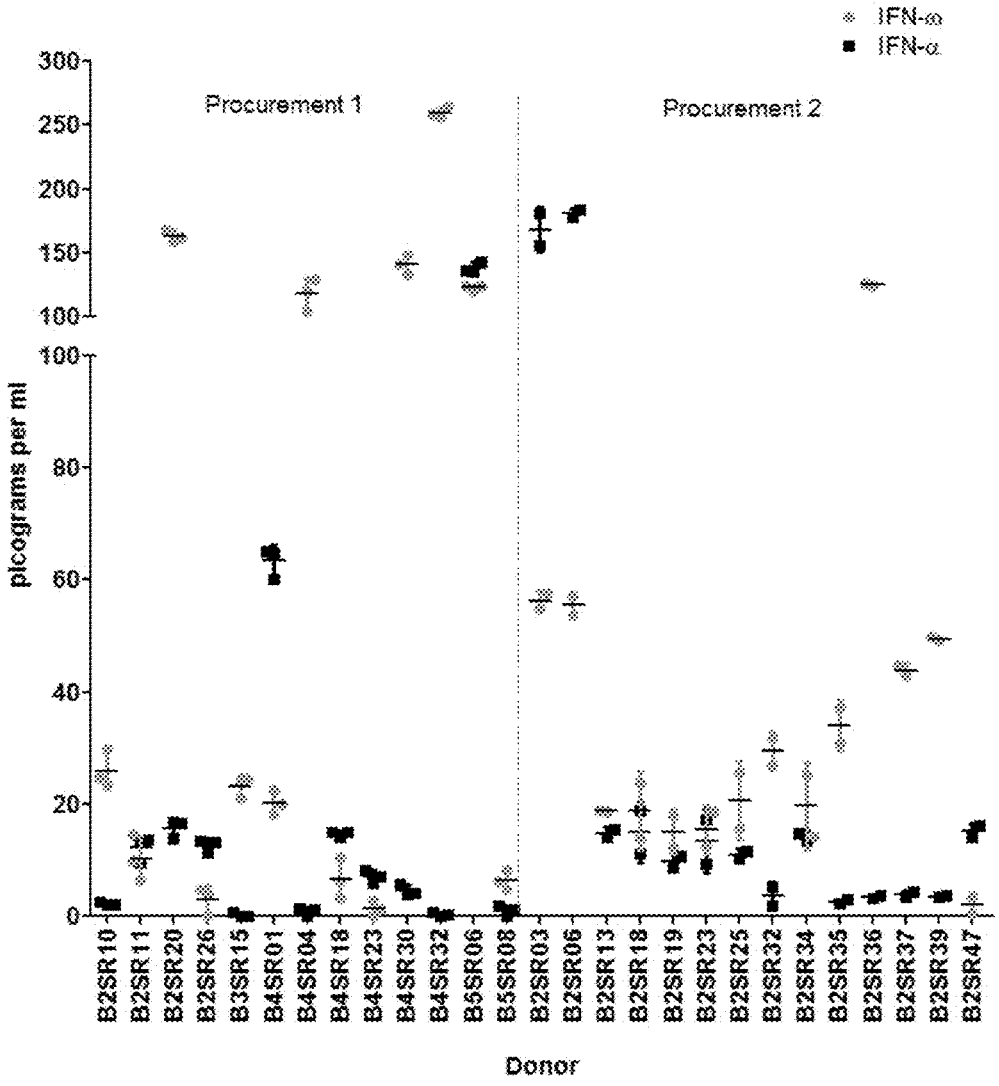

IFN-ω
IFN-α
Procurement 1
Procurement 2
picograms per ml
300
250
200
150
100
100
80
60
40
20
0
B2SR10
B2SR11
B2SR20
B2SR26
B3SR15
B4SR01
B4SR04
B4SR18
B4SR23
B4SR30
B4SR32
B5SR06
B5SR08
B2SR03
B2SR06
B2SR13
B2SR18
B2SR19
B2SR23
B2SR25
B2SR32
B2SR34
B2SR35
B2SR36
B2SR37
B2SR39
B2SR47
Donor

Figure 1B

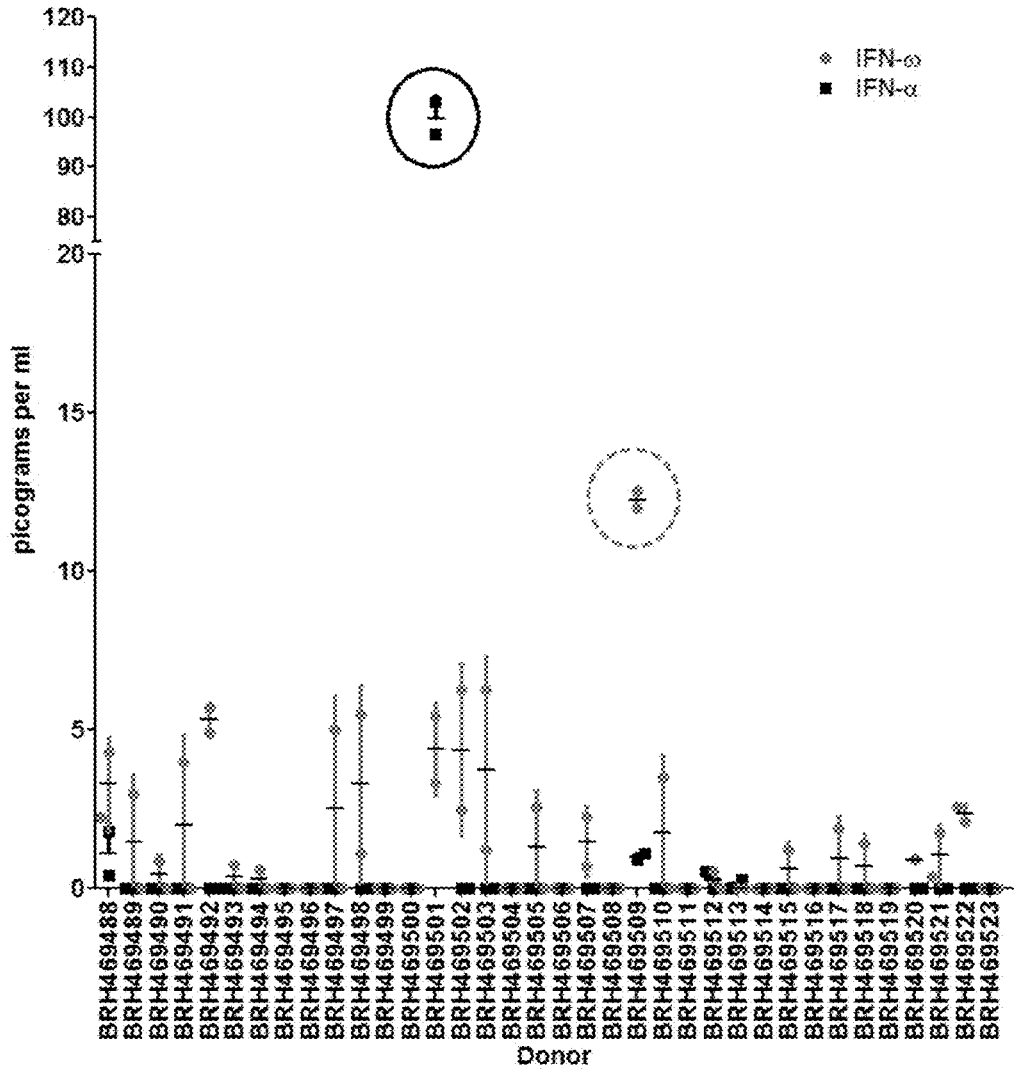

IFN-ω
IFN-α
picograms per ml
120
110
100
90
80
20
15
10
5
0
BRH469488
BRH469489
BRH469490
BRH469491
BRH469492
BRH469493
BRH469494
BRH469495
BRH469496
BRH469497
BRH469498
BRH469499
BRH469500
BRH469501
BRH469502
BRH469503
BRH469504
BRH469505
BRH469506
BRH469507
BRH469508
BRH469509
BRH469510
BRH469511
BRH469512
BRH469513
BRH469514
BRH469515
BRH469516
BRH469517
BRH469518
BRH469519
BRH469520
BRH469521
BRH469522
BRH469523
Donor

Figure 1C

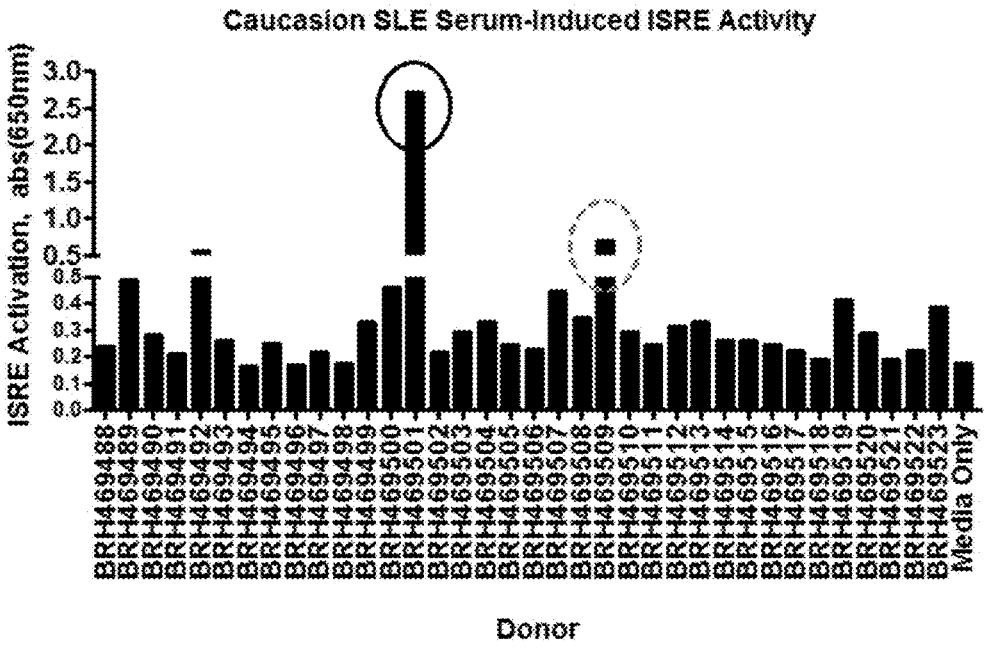

Caucasion SLE Serum-Induced ISRE Activity
ISRE Activation, abs(650nm)
3.0
2.5
2.0
1.5
1.0
0.5
0.5
0.4
0.3
0.2
0.1
0.0
BRH469488
BRH469489
BRH469490
BRH469491
BRH469492
BRH469493
BRH469494
BRH469495
BRH469496
BRH469497
BRH469498
BRH469499
BRH469500
BRH469501
BRH469502
BRH469503
BRH469504
BRH469505
BRH469506
BRH469507
BRH469508
BRH469509
BRH469510
BRH469511
BRH469512
BRH469513
BRH469514
BRH469515
BRH469516
BRH469517
BRH469518
BRH469519
BRH469520
BRH469521
BRH469522
BRH469523
Media Only
Donor

Figure 2

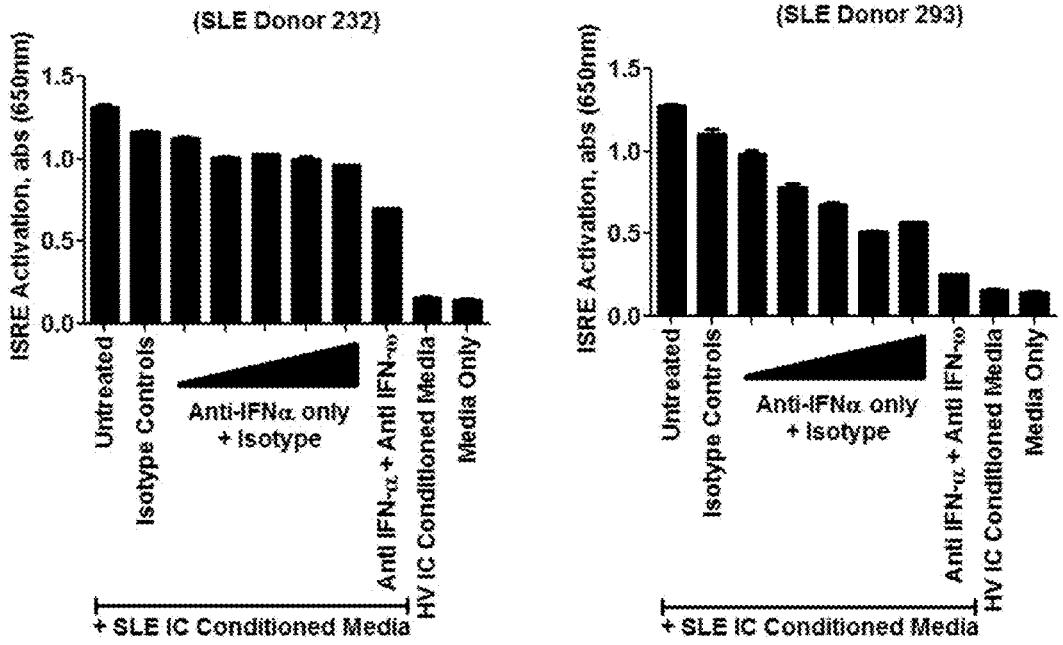

(SLE Donor 232)
ISRE Activation, abs (650nm)
1.5
1.0
0.5
0.0
Untreated
Isotype Controls
Anti-IFNα only
+ Isotype
Anti IFN-α + Anti IFN-ω
HV IC Conditioned Media
Media Only
+ SLE IC Conditioned Media
(SLE Donor 293)
ISRE Activation, abs (650nm)
1.5
1.0
0.5
0.0
Untreated
Isotype Controls
Anti-IFNα only
+ Isotype
Anti IFN-α + Anti IFN-ω
HV IC Conditioned Media
Media Only
+ SLE IC Conditioned Media

Figure 3.

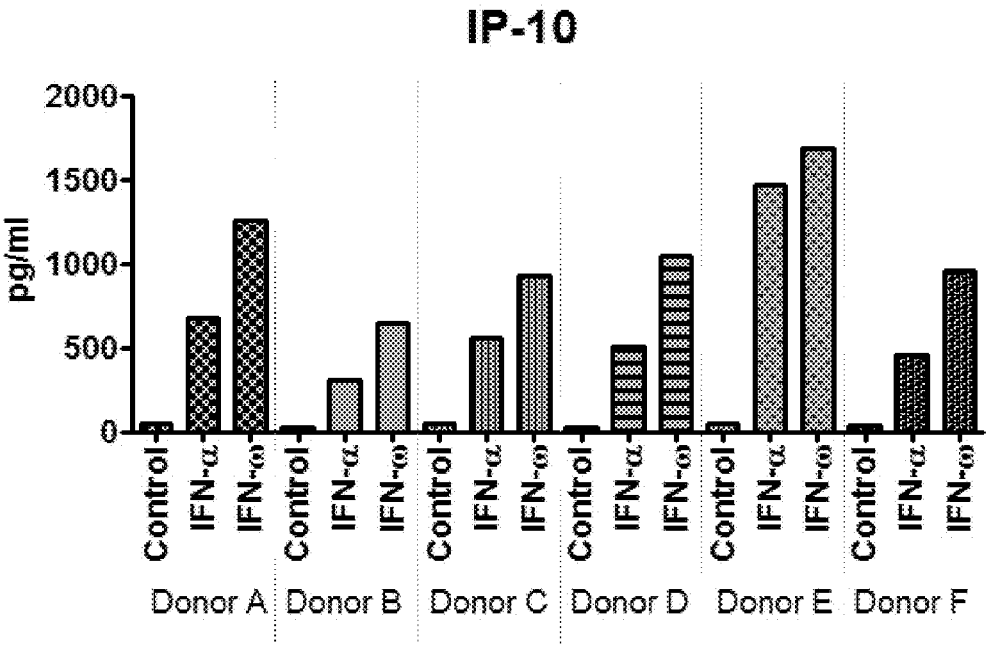

IP-10
pg/ml
2000
1500
1000
500
0
Control
IFN-α
IFN-ω
Donor A
Donor B
Donor C
Donor D
Donor E
Donor F

Figure 4A

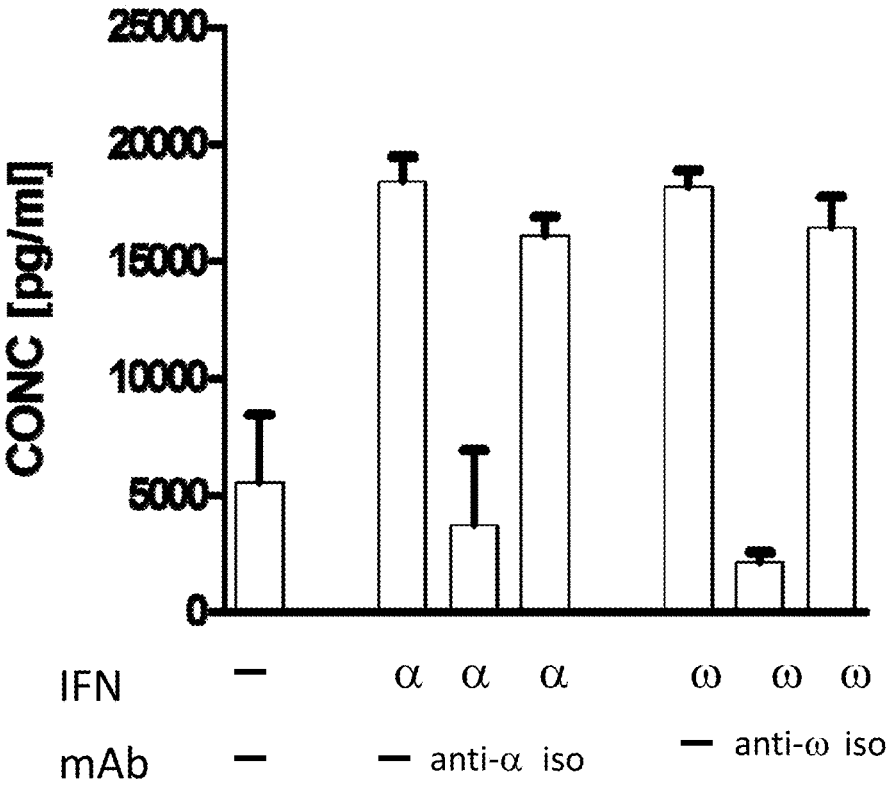

25000
20000
15000
10000
5000
0
CONC [pg/ml]
IFN
mAb
α α α
ω ω ω
anti-α iso
anti-ω iso

Figure 4B.

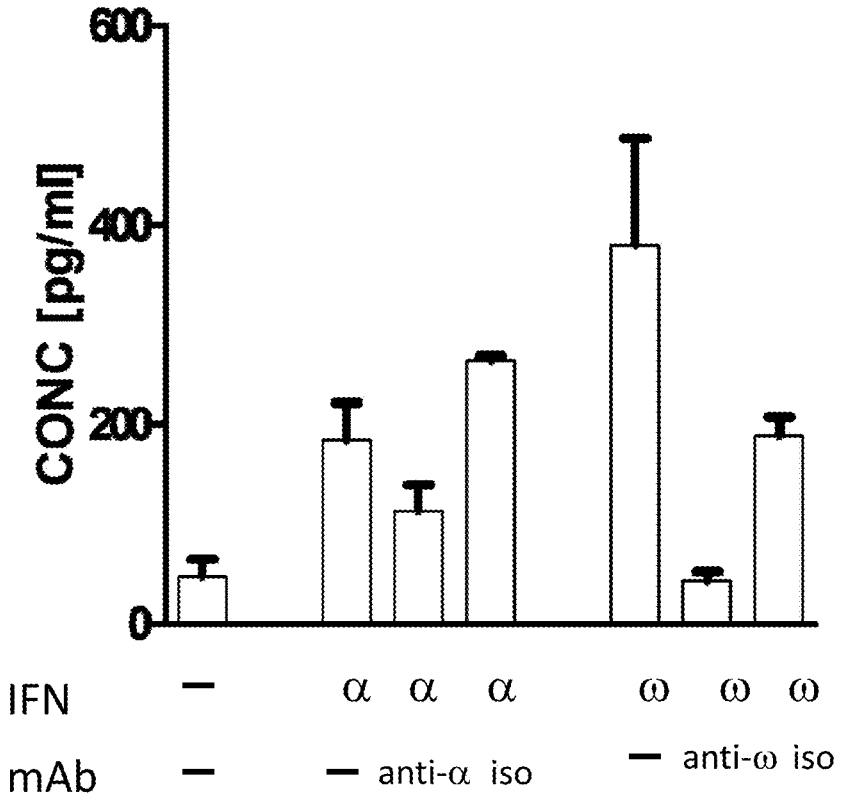


Figure 5A.

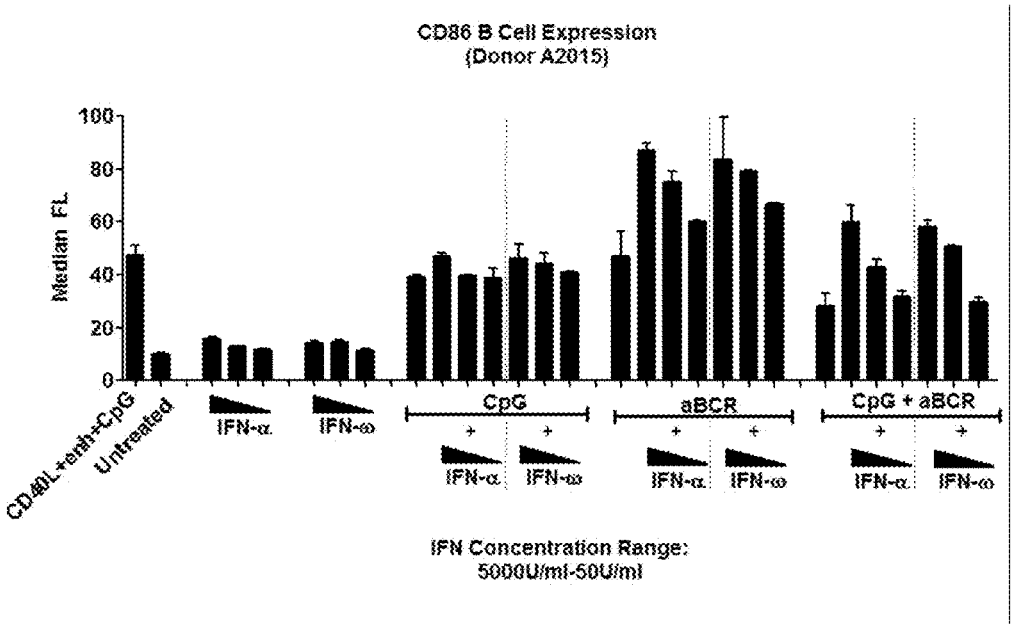

CD86 B Cell Expression
(Donor A2015)
Median FL
100
80
60
40
20
0
CD40L+enh+CpG
Untreated
IFN-α
IFN-ω
CpG
aBCR
CpG + aBCR
+
IFN-α
IFN-ω
IFN Concentration Range:
5000U/ml-50U/ml

Figure 5B.

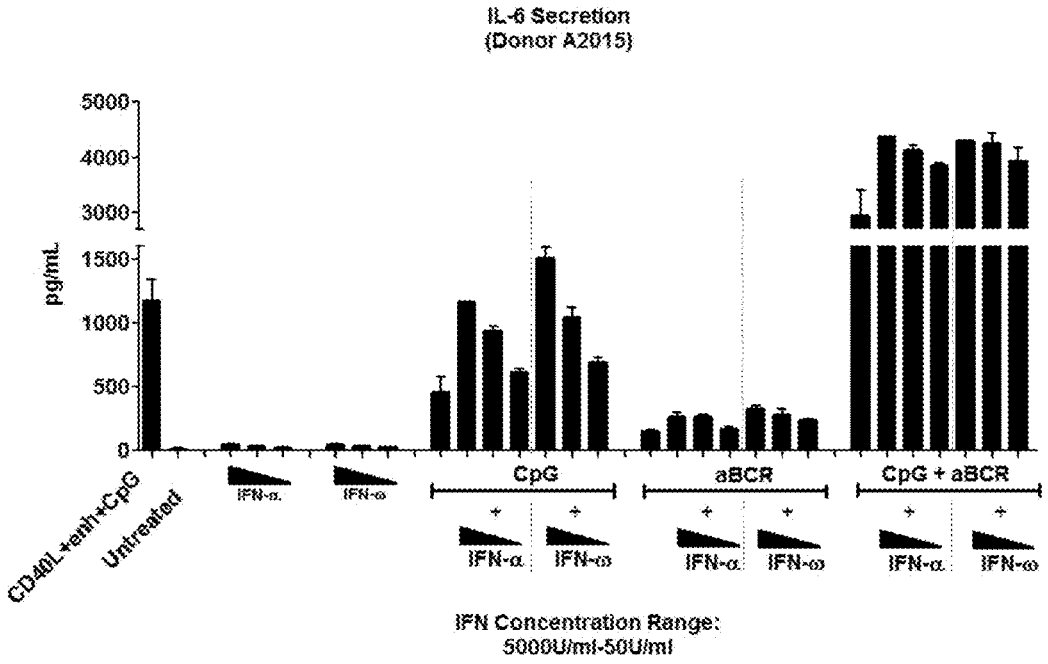

IL-6 Secretion
(Donor A2015)
pg/mL
5000
4000
3000
1500
1000
500
0
CD40L+anti-CpG
Untreated
IFN-α
IFN-ω
CpG
aBCR
CpG + aBCR
+
IFN-α
IFN-ω
IFN Concentration Range:
5000U/ml-50U/ml

Figure 6.

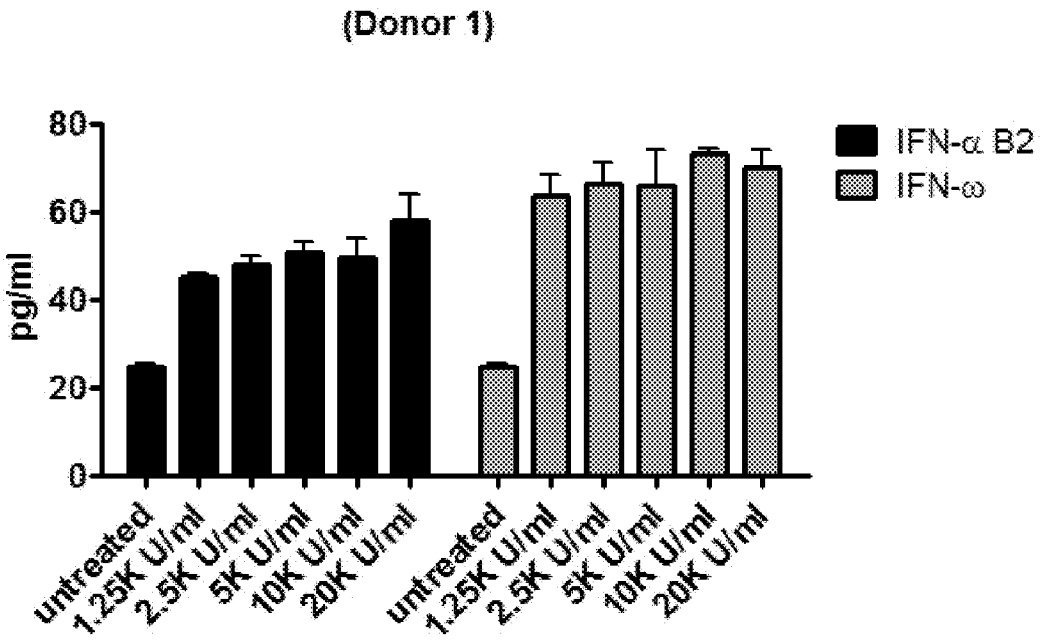

(Donor 1)
80
60
40
20
0
pg/ml
IFN-α B2
IFN-ω
untreated
1.25K U/ml
2.5K U/ml
5K U/ml
10K U/ml
20K U/ml
untreated
1.25K U/ml
2.5K U/ml
5K U/ml
10K U/ml
20K U/ml

Figure 7A.

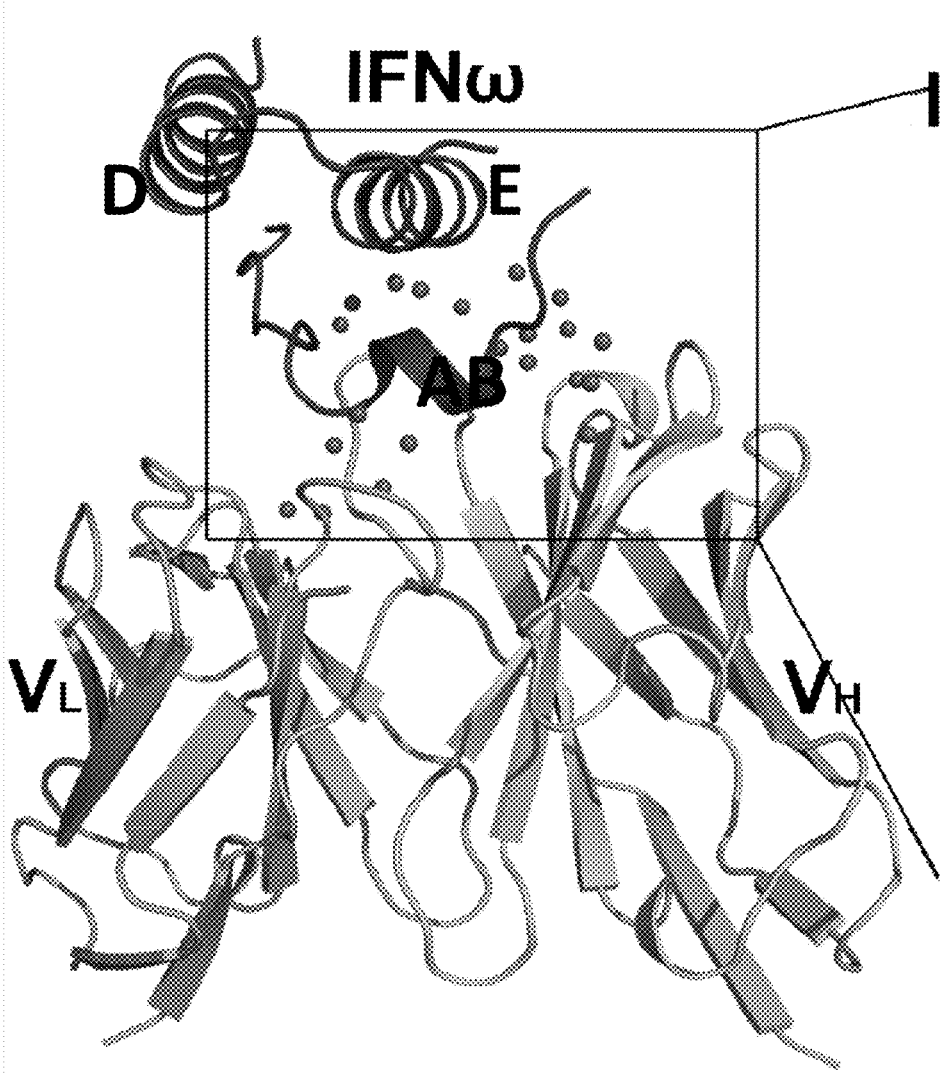


Figure 7B.

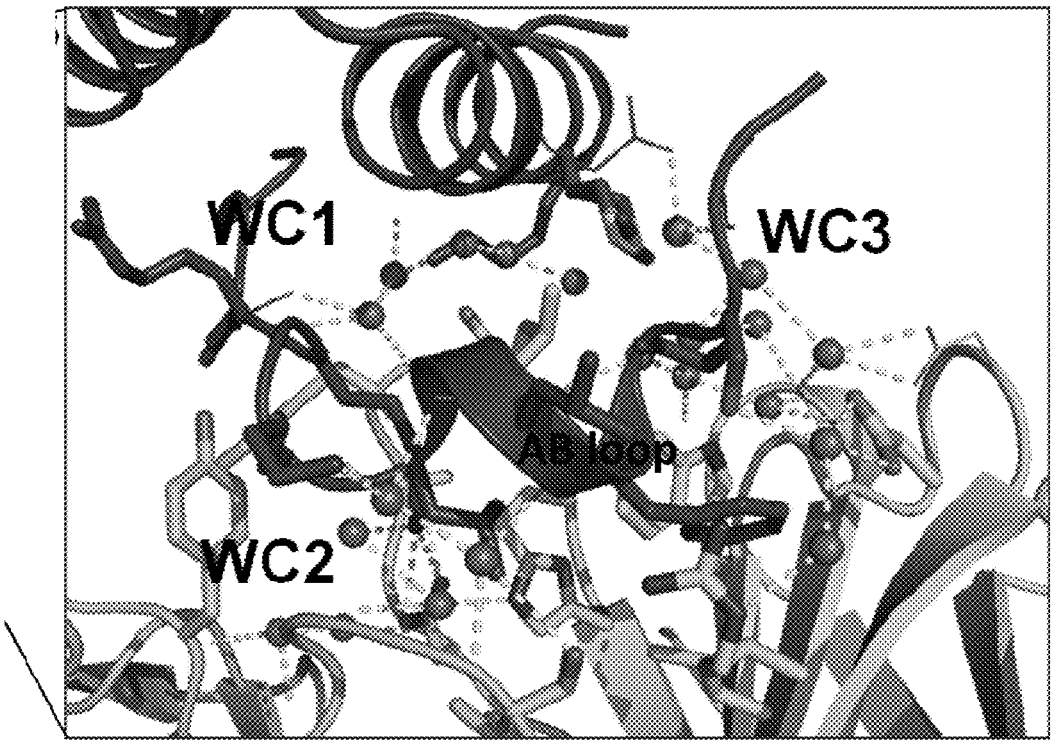


Figure 8A.

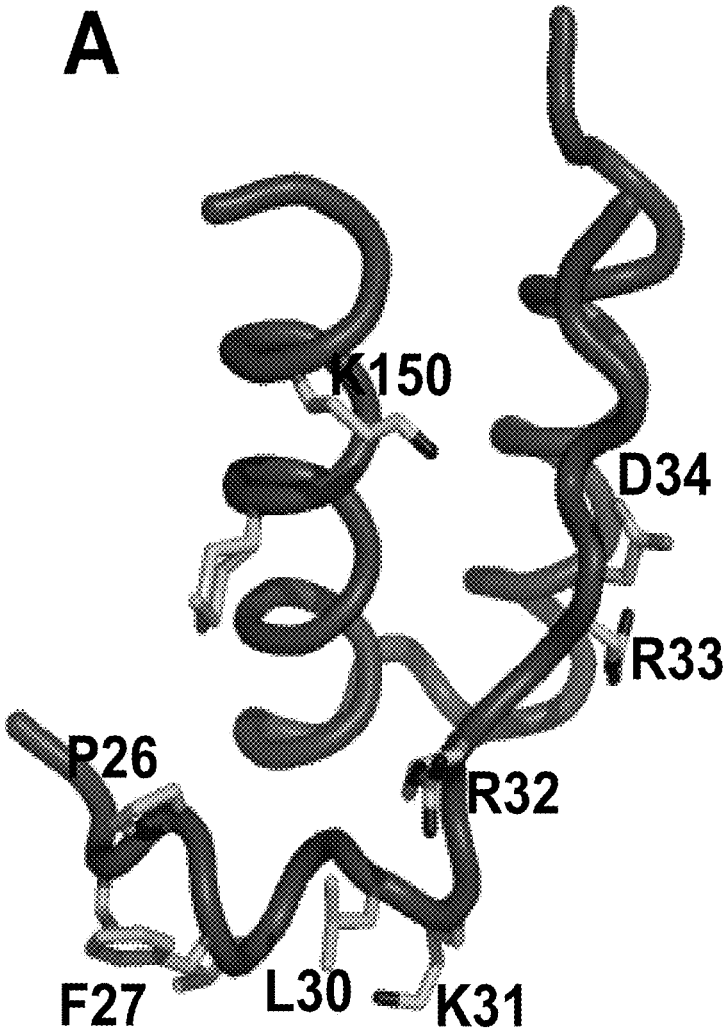


Figure 8B.

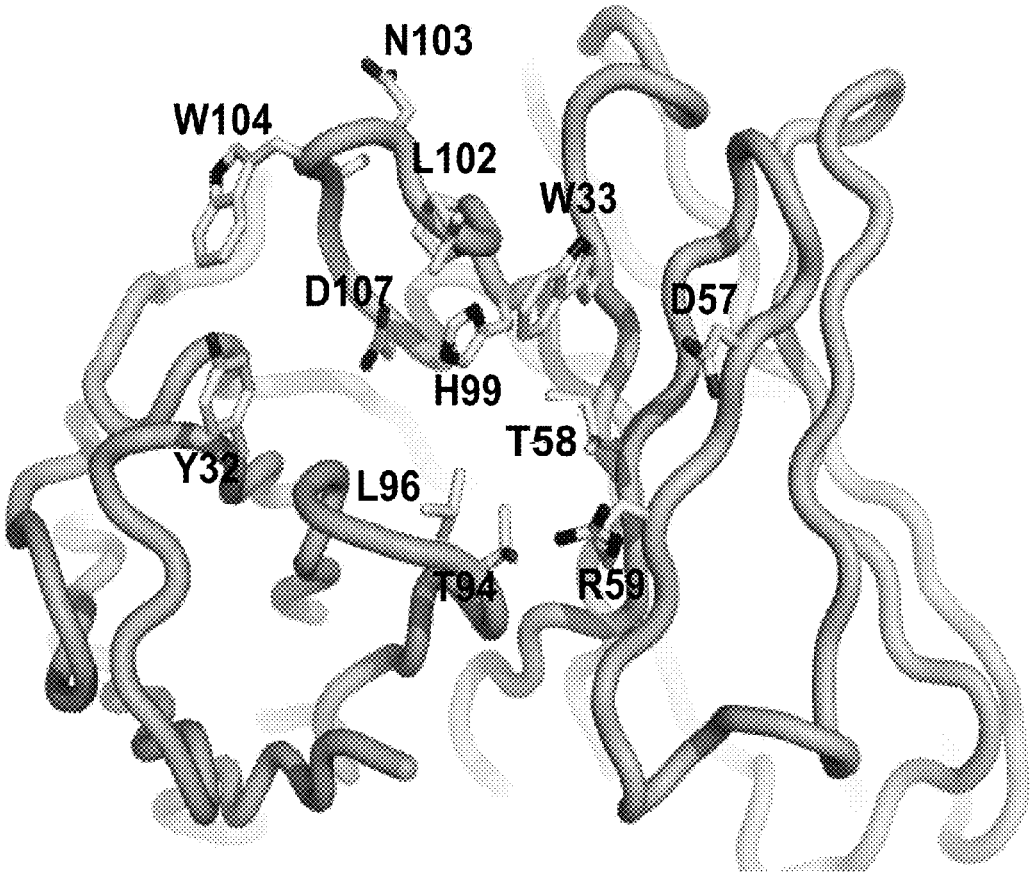
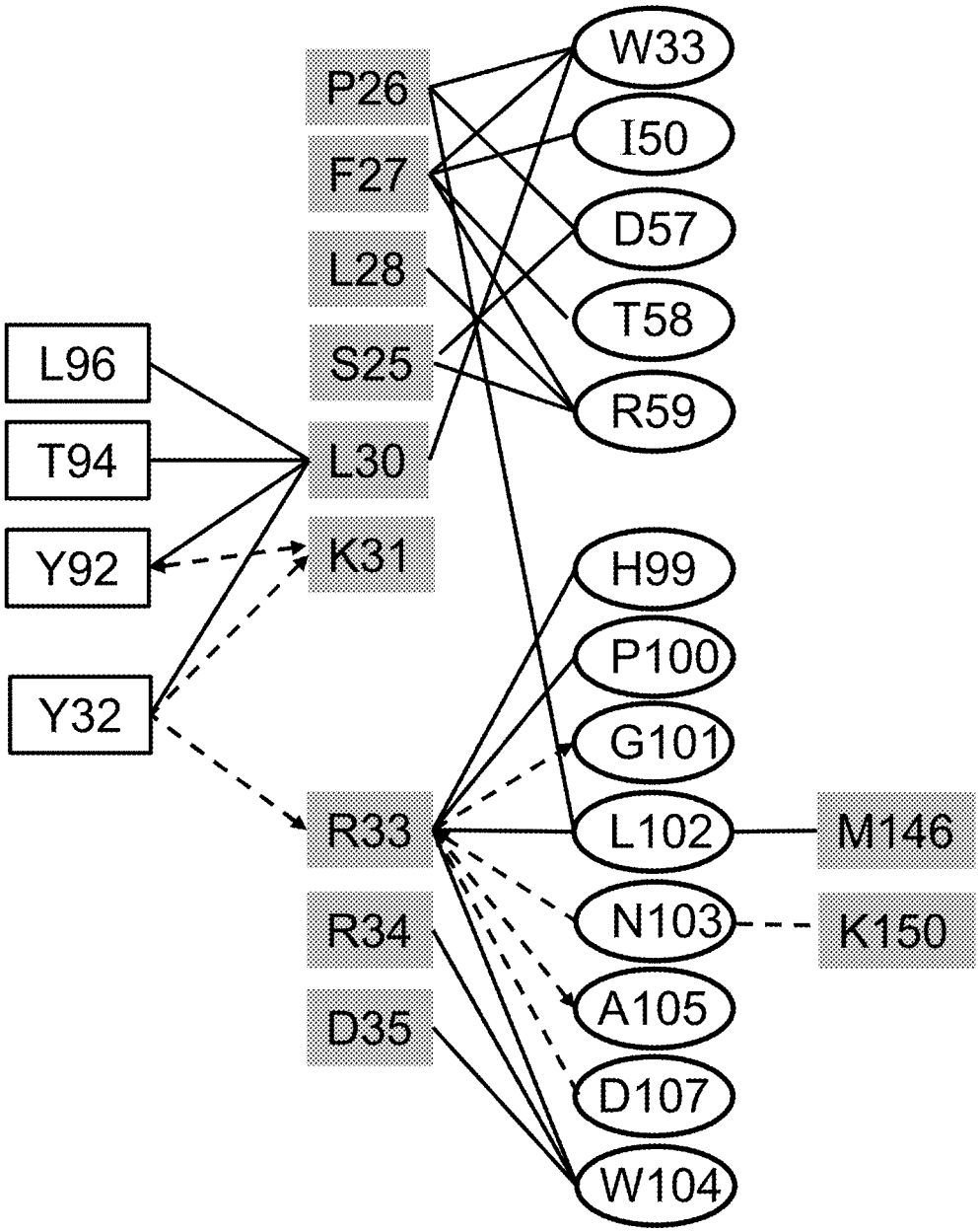


Figure 8C.


P26
F27
L28
S25
L30
K31
R33
R34
D35
L96
T94
Y92
Y32
W33
I50
D57
T58
R59
H99
P100
G101
L102
N103
A105
D107
W104
M146
K150

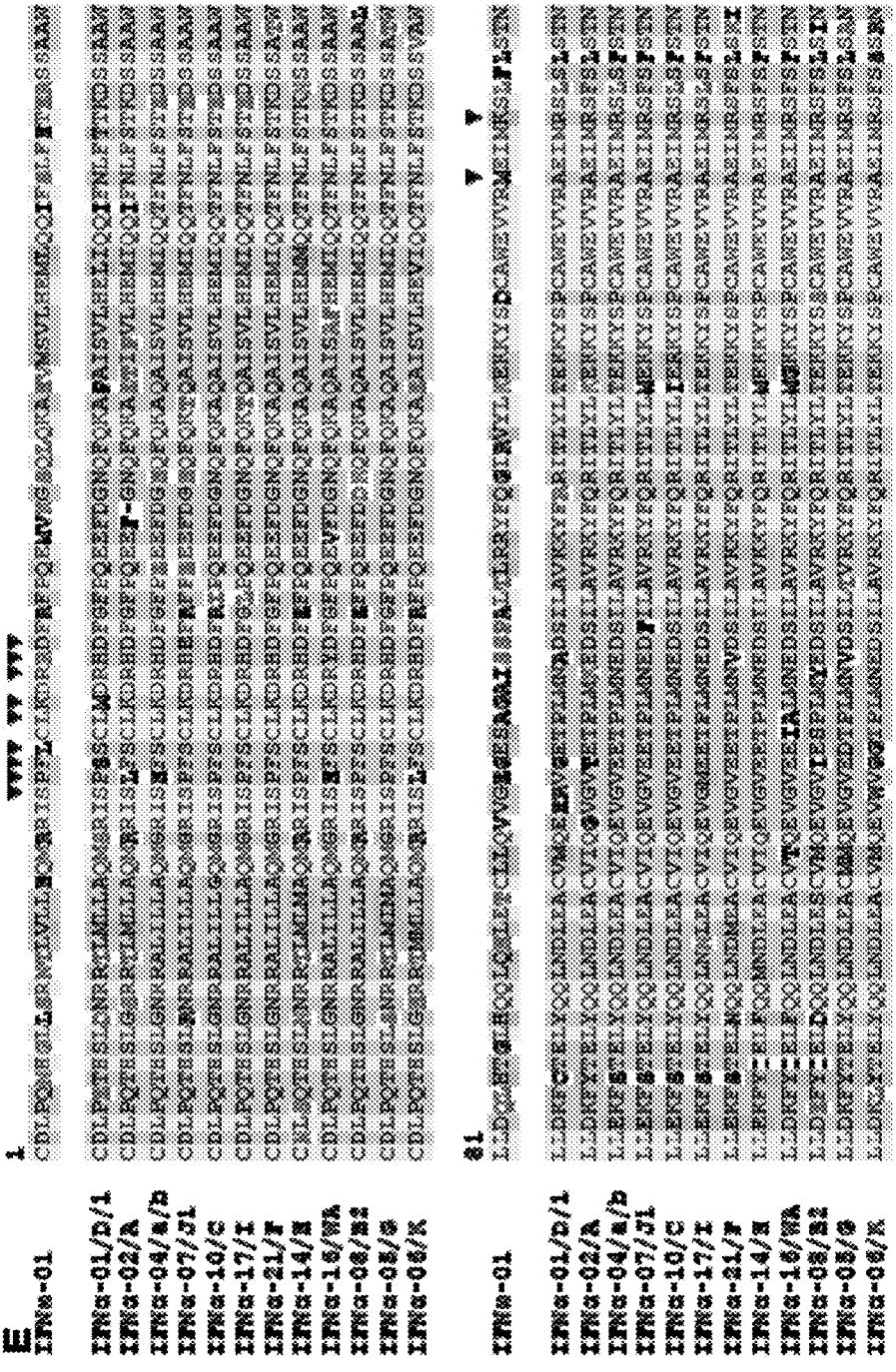


Figure 9.

Figure 10.

mAb	ISRE IC50 (pM)													
	αA	αB2	αC	αD	αF	αG	αH2	αI	αJ1	αK	αWA	α4a	β	ω
IFWM3308	94	230	996	NT	155	167	32	478	363	59	894	295	NN	40
IFWM3307	73	247	583	NN	170	95	88	752	328	95	600	501	NN	100
IFWM3410	NT	211	168	NN	77	55	33	183	217	41	538	192	NN	89
IFWM3322	31	121	306	NN	117	83	46	460	169	71	382	352	NN	59
IFWM3385	63	158	272	NN	66	77	29	225	251	65	839	414	NN	68
IFWM3416	81	250	112	NN	64	49	35	158	61	43	779	201	NN	40
IFWM3310	50	43	196	NN	111	73	45	258	166	96	473	169	NN	81
IFWM3400	35	86	138	NN	43	35	15	137	154	35	376	220	NN	29
IFWM3321	29	87	266	NN	54	34	28	301	114	46	267	295	NN	38
IFWM3522	57	96	77	NT	225	57	34	124	134	29	185	163	NT	53
IFWM3524	19	31	72		25	21						84		22
IFWM3320	45	18	392	NT	54	82	23	355	213	34	633	166	NN	53
IFWM3304	29	39	117	NN	62	47	42	157	126	57	237	112	NN	31
IFWM3520	17	21	31		18	16						23		12
IFWM3399	43	62	189	NN	29	29	13	18	106	32	189	111	NN	27
IFWM3314	29	33	157	NN	58	57	40	163	86	65	188	137	NN	32
IFWM3331	18	80	98	NN	48	27	33	198	94	28	109	117	NN	50
IFWM3405	40	99	68	NN	35	26	16	72	26	22	216	86	NN	19
IFWM3442	77	75	40	NN	14	16	16	8	20	2140	36	25	NN	18
IFWM3525	23	25	34	NT	82	19	15	240	84	7	66	42	NT	19
IFWM3423	12	11	12	NN	8	9	4	4	6	9	10	8	NN	6
IFWM3444	28	27	55	NN	16	15	9	9	24	19	46	23	NN	9
IFWM3421	13	16	20	NN	11	18	8	17	14	18	14	15	NN	8

NN= non-neutralizing

Figure 11A.

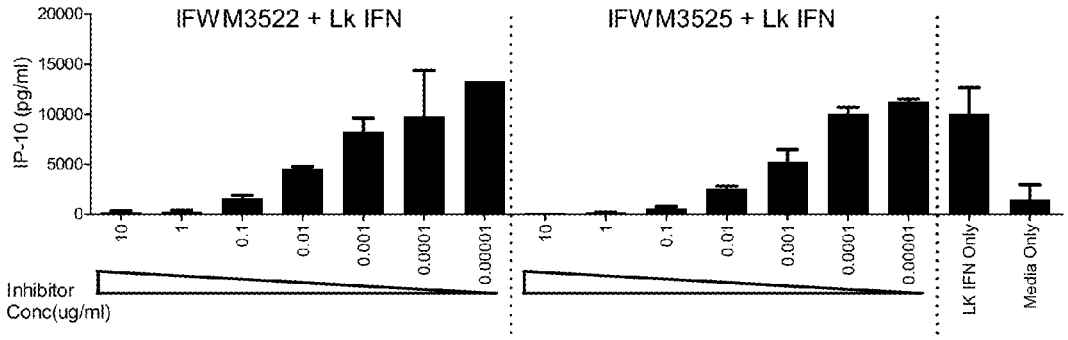

IFWM3522 + Lk IFN
IFWM3525 + Lk IFN
IP-10 (pg/ml)
20000
15000
10000
5000
0
10
1
0.1
0.01
0.001
0.0001
0.00001
Inhibitor Conc(ug/ml)
LK IFN Only
Media Only

Figure 11B.

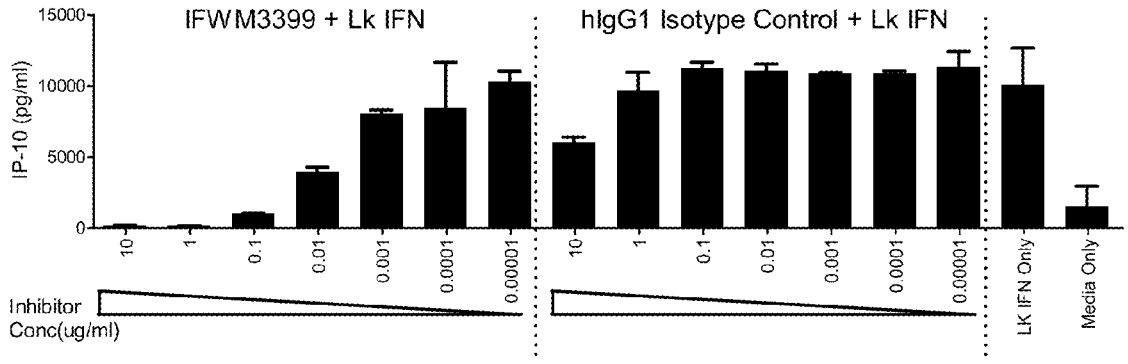

IFWM3399 + Lk IFN
hIgG1 Isotype Control + Lk IFN
IP-10 (pg/ml)
15000
10000
5000
0
10
1
0.1
0.01
0.001
0.0001
0.00001
Inhibitor Conc(ug/ml)
LK IFN Only
Media Only

Figure 12A.

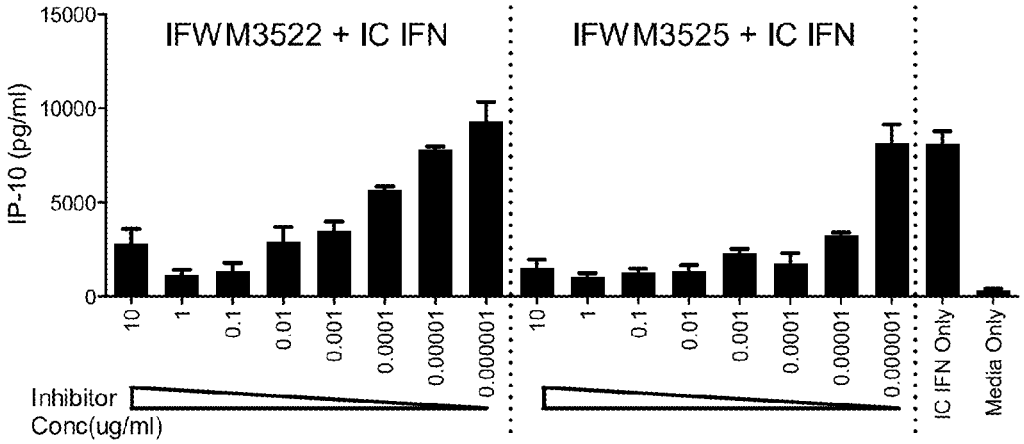

IFWM3522 + IC IFN
IFWM3525 + IC IFN
IP-10 (pg/ml)
15000
10000
5000
0
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
IC IFN Only
Media Only
Inhibitor Conc(ug/ml)

Figure 12B.

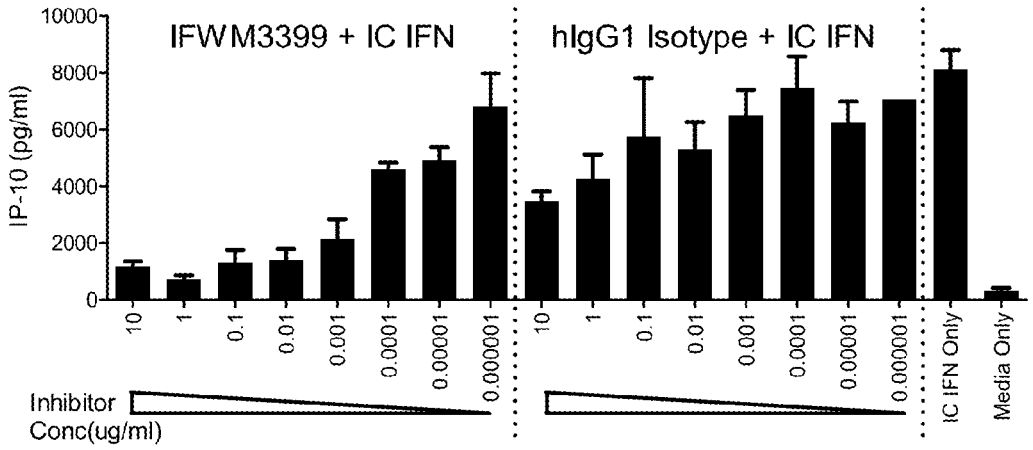

IFWM3399 + IC IFN
hIgG1 Isotype + IC IFN
IP-10 (pg/ml)
10000
8000
6000
4000
2000
0
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
IC IFN Only
Media Only
Inhibitor
Conc(ug/ml)

Figure 13A.

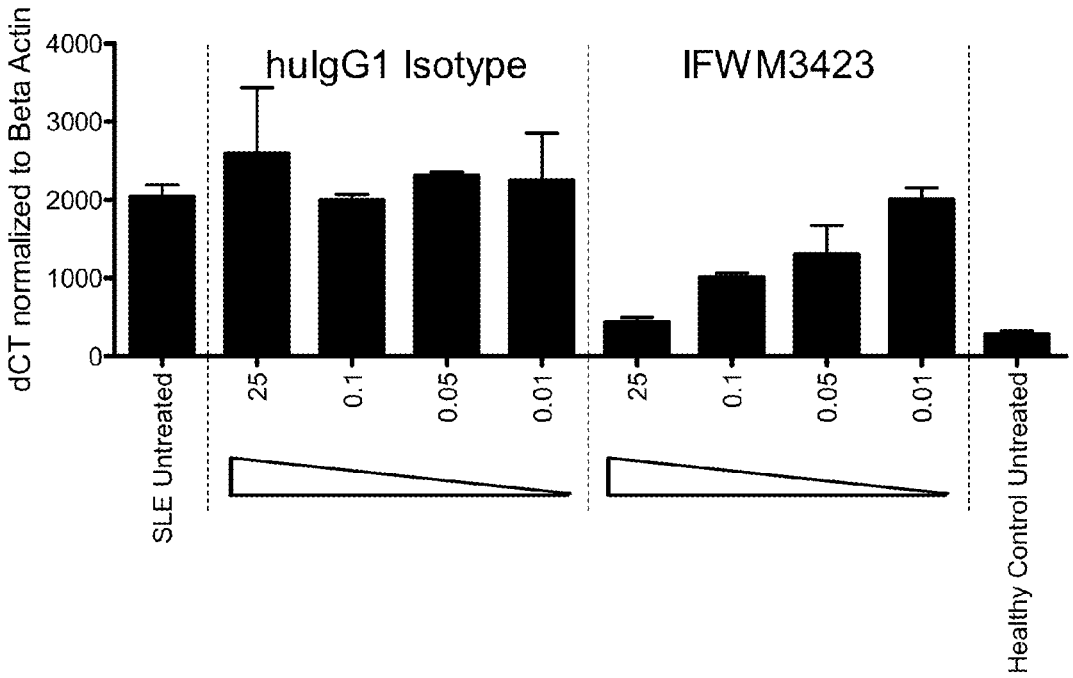

dCT normalized to Beta Actin
4000
3000
2000
1000
0
huIgG1 Isotype
IFWM3423
SLE Untreated
25
0.1
0.05
0.01
25
0.1
0.05
0.01
Healthy Control Untreated

Figure 13B.

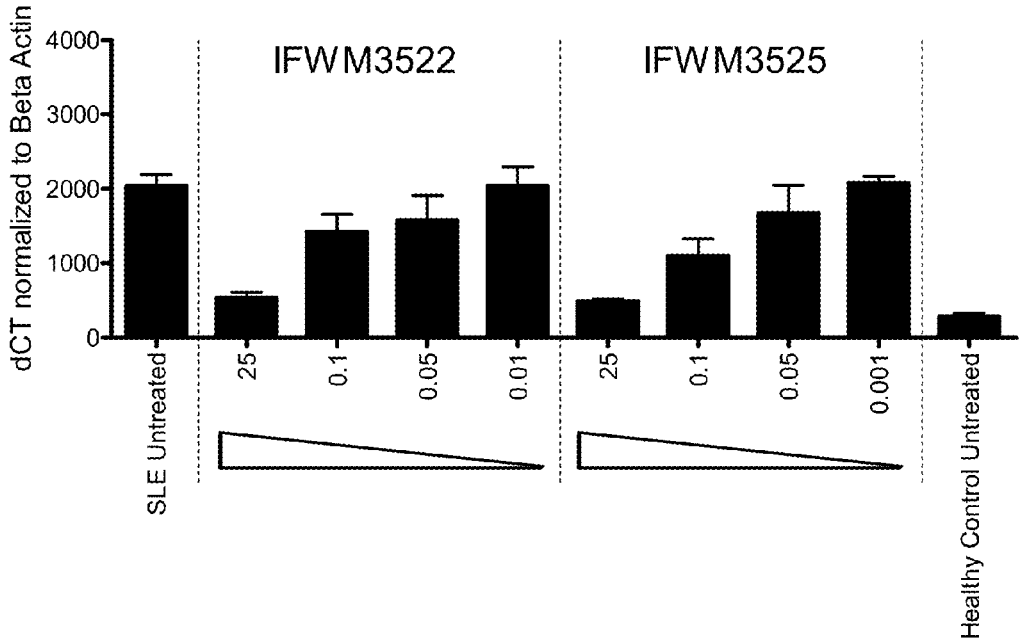

dCT normalized to Beta Actin
4000
3000
2000
1000
0
IFWM3522
IFWM3525
SLE Untreated
25
0.1
0.05
0.01
25
0.1
0.05
0.001
Healthy Control Untreated

Figure 14A.

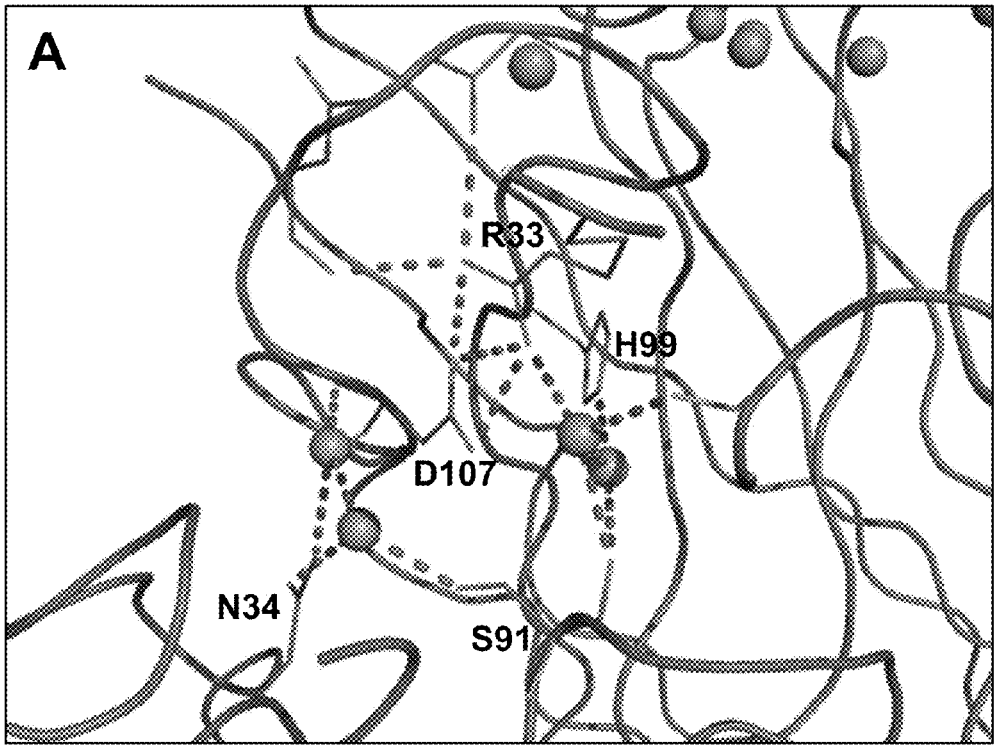


Figure 14B.

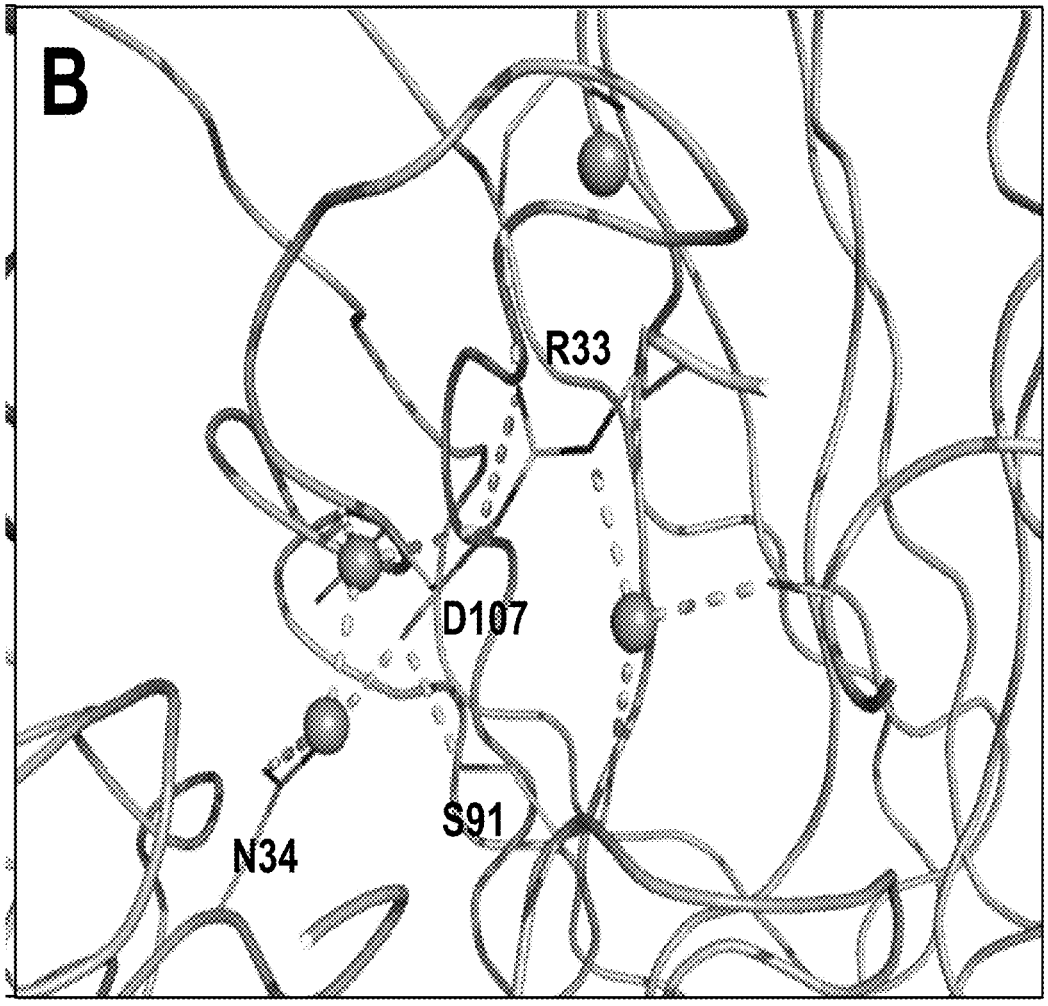


Figure 14C.

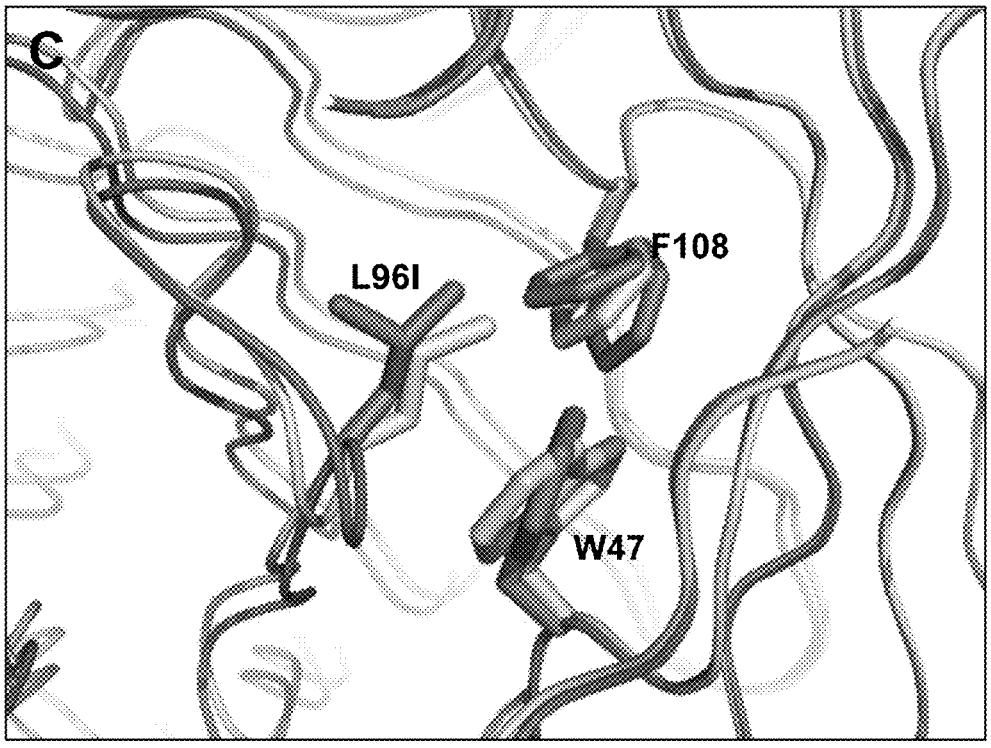


Figure 14D.

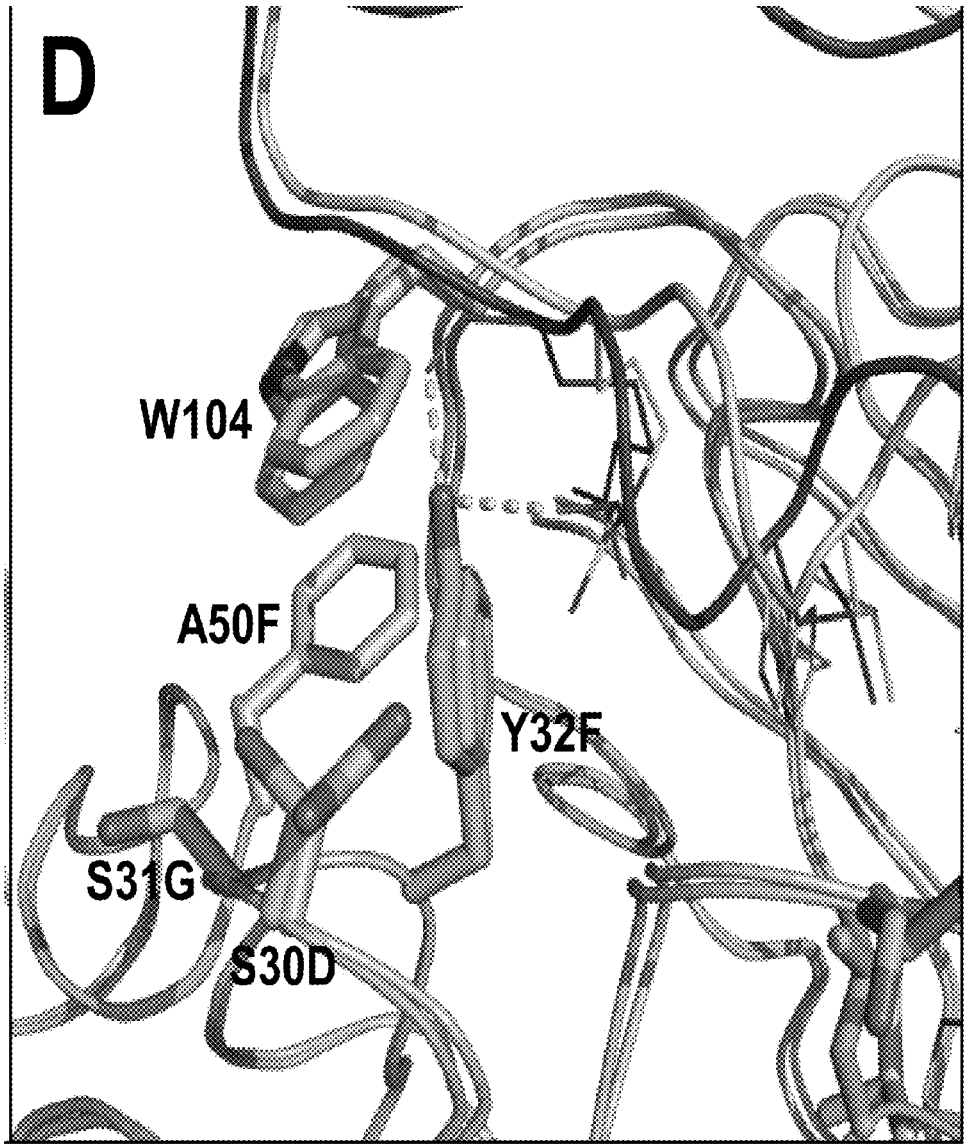


Figure 15.

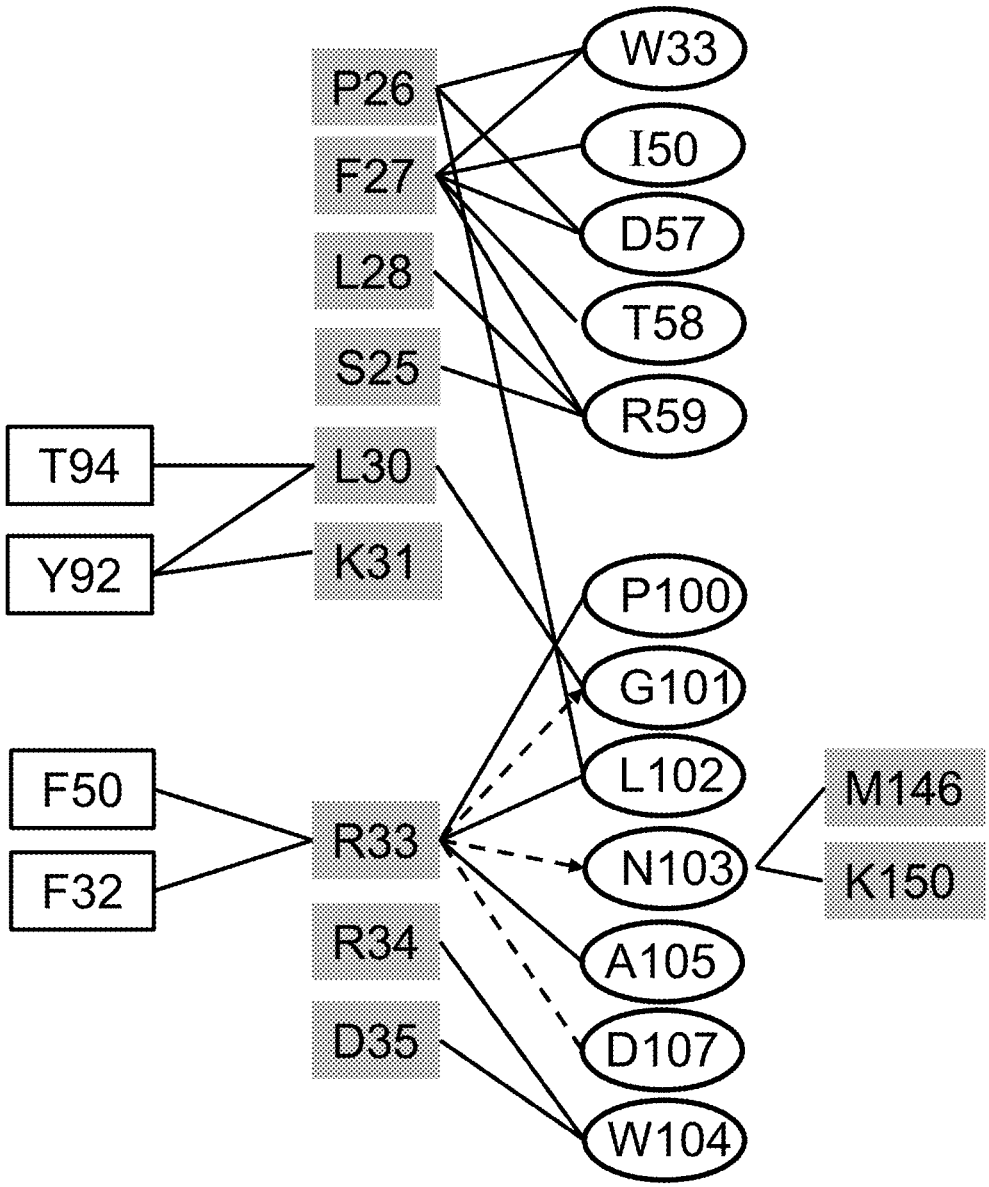
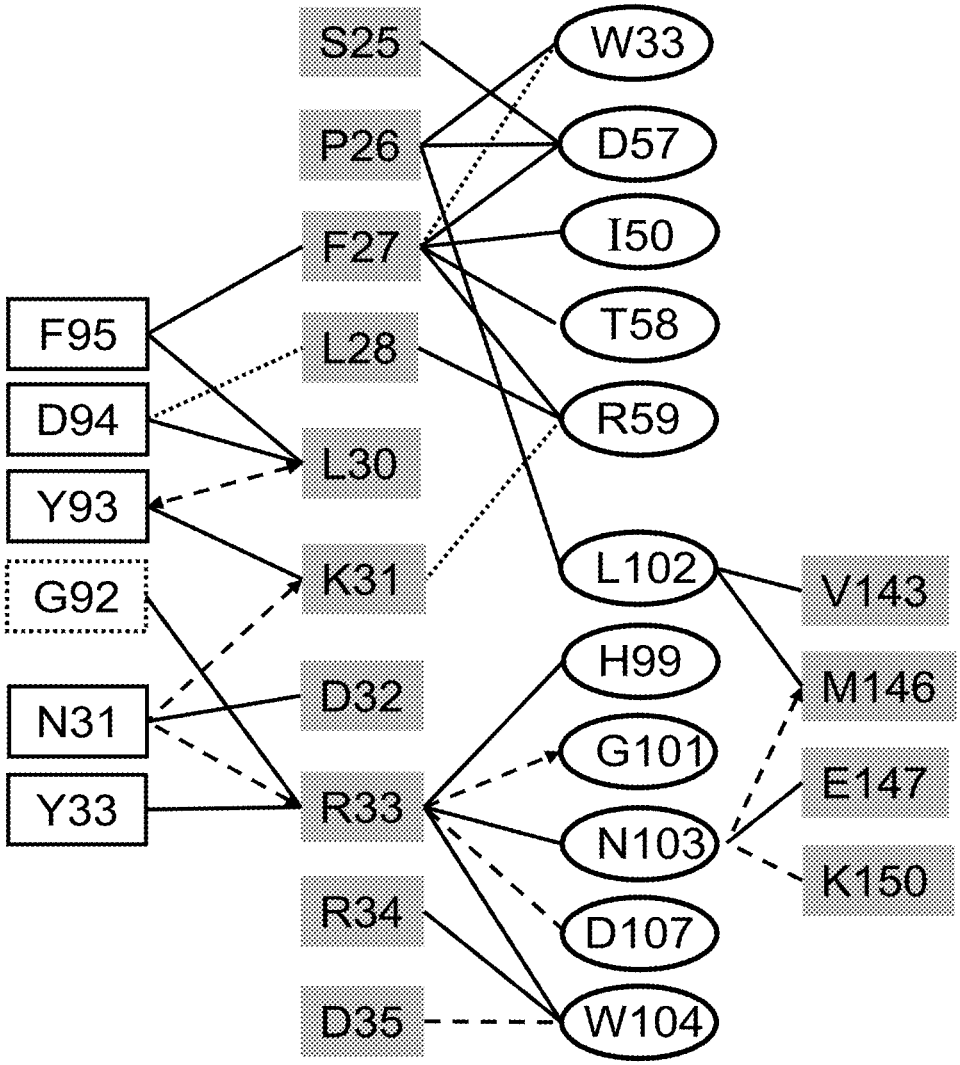

W33
P26
I50
F27
D57
L28
T58
S25
R59
T94
L30
Y92
K31
P100
G101
F50
L102
M146
R33
N103
K150
F32
R34
A105
D35
D107
W104

Figure 16.


S25
P26
F27
L28
L30
K31
D32
R33
R34
D35
W33
D57
I50
T58
R59
L102
H99
G101
N103
D107
W104
V143
M146
E147
K150
F95
D94
Y93
G92
N31
Y33

INTERFERON ALPHA AND OMEGA ANTIBODY ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application Ser. No. 62/015,765, filed 23 Jun. 2014. The entire contents of the aforementioned application are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0002] The present invention relates to antibodies that broadly neutralize interferon-α and interferon-ω, polynucleotides encoding the antibodies or fragments, and methods of making and using the foregoing.

BACKGROUND OF THE INVENTION

[0003] Type I interferons (IFNs) (IFN-I) are a family of cytokines that signal through a ubiquitously expressed heterodimeric receptor IFNAR (heterodimer of IFNAR1 and IFNAR2) resulting in antiviral, antiproliferative and immunomodulatory effects. In humans, type I IFN is composed of at least 12 IFN-α protein subtypes and 1 subtype each for IFN-β, IFN-ε, IFN-κ, and IFN-ω. IFN-I release occurs in response to both microbial and sterile ligands. Upon receptor binding, IFN-I initiates a signaling cascade through activation of JAK1 and TYK2 leading to the phosphorylation of several STAT family members including STATs 1-6. STAT1 and STAT2 activation leads to the formation of a complex with IFN-regulatory factor 9 (IRF9) and this complex, also known as the IFN-stimulated gene factor 3 (ISGF3) complex, binds to IFN-stimulated response elements (ISREs) in the nucleus resulting in the transcription of many interferon-stimulated genes (ISGs) including IRF7 and CXCL10 (IP-10) (Gonzalez-Navajas et al., *Nature reviews. Immunology* 12, 125 (February 2012). IFN-I also modulates cellular function through other pathways including the v-crk sarcoma virus CT10 oncogene homolog (avian)-like (CRKL), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), and through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) (Hervas-Stubbs et al., *Clinical cancer research: an official journal of the American Association for Cancer Research* 17, 2619 (May 1, 2011)).

[0004] Several immune-mediated inflammatory diseases or autoimmune diseases, such as lupus, including Systemic Lupus Erythematosus (SLE) and cutaneous lupus erythematosus (CLE), type I diabetes, psoriasis, Sjogren's disease, systemic sclerosis, rheumatoid arthritis, immune thrombocytopenia (ITP), Aicardi-Goutieres syndrome (AGS), myositis, common variable immune deficiency (CVID) and autoimmune thyroid disease are associated at least in a sub-population of patients with overexpression of IFN-inducible gene transcripts commonly called the IFN signature present in whole blood and/or tissue, or with elevated IFN-I.

[0005] SLE is a chronic autoimmune or immune-mediated inflammatory disease in which the production of pathogenic autoantibodies and immune complexes result in tissue damage across multiple organ systems. The disease displays a broad range of symptoms with heterogeneous clinical presentation and may include systemic, cutaneous, renal, musculoskeletal, neurological and hematological manifestations. SLE varies greatly in severity and is chronic, remitting or relapsing with flares of activity cycling with periods of improvement or remission that may last weeks, months, or years. IFN-α is elevated in SLE patients and is believed to promote a loss of tolerance to self. IFN-α has been shown to contribute to sustained dendritic cell activation and thus antigen presentation, and suppression of Treg function contributing to SLE. IFN-α also induces BLyS expression, a target for the marketed SLE therapeutic BENLYSTA™. A number of polymorphisms associated with production or response to IFN-I have been identified and account for over half of confirmed polymorphisms associated with SLE (Ghodke-Puranik & Niewold , *International journal of clinical rheumatology* 8, doi:10.2217/ijr.13.58 (2013)). Antibodies neutralizing various IFN-α subtypes (pan-IFN-α antibodies) are being evaluated in clinical trials for SLE (see, for example, Int. Pat. Publ. No. WO02/066649, Int Pat. Publ. No. WO05/059106, Int. Pat. Publ. No. WO06/086586, Int. Pat. Publ. No. WO09/135861).

[0006] IFN-ω constitutes approximately 15% of the total IFN-I activity in human leukocyte IFN preparations produced after viral infection (Adolf, *Virology* 175, 410 (April 1990). IFN-ω gene expression has been reported to be elevated in SLE patients (Han et al., *Genes and immunity* 4, 177 (April 2003); Yao et al., Hum Genomics Proteomics 2009, (2009)), and the ability of IFN-ω to induce DC differentiation has been reported (Walker and Tough, *European journal of immunology* 36, 1827 (July 2006)). The anti-IFN-α antibodies currently in clinical trials (sifalimumab (MEDI-545), rontalizumab and AGS-009) do not neutralize IFN-ω. Clinical trial data with these antibodies indicate partial reduction of the type I IFN signature in patients after treatment with anti-IFN-α antibodies (Merrill et al., Ann Rheum Dis 70:1905-1913, 2011; Yao et al., Arthritis Rheum 60:1785-1796, 2009), and Phase 2 trial data with rontalizumab (a pan-anti-IFN-α antibody) indicated improvement in signs and symptoms of SLE, flare rates, and steroid burden at week 24 in a pre-specified biomarker defined group of Interferon Signature Metric (ISM)-Low moderate to severely active lupus subjects. No efficacy was seen in patients having higher levels of IFN-inducible gene expression pre-defined as ISM-High (Kalunian et al., 2012 ACR/ARHP Annual Meeting; Abstract #2622, 2012).

[0007] In addition to anti-IFN antibodies, anti-IFNAR1 antibodies are being investigated for the treatment of lupus (Wang et al., 2013; Clinical Pharmacology & Therapeutics accepted article preview 14 Feb. 2013; doi: 10.1038/clpt.2013.35). IFNAR1 blockage is likely to abolish IFN signaling induced by all type I IFNs, including IFN-β. IFN-β may play a more critical role in antiviral defense, as specific deletion of the gene encoding IFN-β incurs substantial susceptibility to a host of viruses when compared to similarly exposed mice having functional IFN-β (Lazear et al., J Virol 85:7186-7194; Deonarain et al., J Virol 74(7): 3404-340, 2000; Deonarain et al., Circulation 110: 3540-3543, 2004; Gerlach, et al., J Virol 80: 3438-3444, 2006). Therefore, anti-IFNAR1 antibodies may increase the risk of side effects.

[0008] Current standard of care for SLE includes corticosteroids, antimalarial drugs, immunosuppressants or B cell modulators. These therapeutics may exhibit toxicity and other serious side effects, and may not be suitable for treatment of all lupus patients. Thus, there is a need for additional therapeutic treatments for lupus and other immune-mediated inflammatory or autoimmune diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. **1**A shows IFN-ω and IFN-α levels (pg/ml) in plasma from Chinese SLE patients. Horizontal bars in the figure indicate mean ELISA value of replicate samples, vertical bars indicate standard deviation (SD).

[0010] FIG. **1**B shows IFN-ω and IFN-α levels (pg/ml) in serum from Caucasian SLE patients. The dark solid circle indicates the highest IFN-α levels and the dotted line circle indicate the highest IFN-ω plasma levels across the various donors. Horizontal bars in the figure indicate mean ELISA value of replicate samples, vertical bars indicate SD.

[0011] FIG. **1**C shows that patient serum activates downstream interferon signaling pathways measured using ISRE reporter gene assay. The donor exhibiting the greatest amount of IFN-α protein (dark solid circle) and IFN-ω (dotted line circle) also demonstrated the greatest levels of ISRE induction in the reporter gene assay. The results are readings from a single well for each serum sample.

[0012] FIG. **2** shows inhibition of SLE immune complex-induced IFN with increasing concentration (0.4-100 μg/ml) of anti-IFN-α antibody alone or at 100 μg/ml in combination with anti-IFN-ω antibody (20 μ/ml). SLE immune complexes (SLE IC) were prepared from two different donors (SLE Donor 232 or 293). Combined blockage of IFN-α and IFN-ω resulted in enhanced suppression of SLE IC-induced IFN activity, as measured using the ISRE assay. HV IC conditioned media=conditioned media from PBMCs stimulated with immune complexes from healthy donors.

[0013] FIG. **3** shows induction of IP-10 secretion from PBMCs from 6 healthy individuals stimulated with IFN-αA or IFN-ω as indicated.

[0014] FIG. **4**A shows secretion of IFN-γ by $CD4^+$ T cells in the presence of DCs differentiated in the presence of IFN-ω, IFN-α, IFN-ω and anti-IFN-ω antibody, or IFN-α and anti-IFN-α antibody, or isotype control (iso) as indicated. DCs differentiated in the presence of either IFN-ω or IFN-α induced activation of $CD4^+$ T cells to a same degree, whereas DCs differentiated in the presence of anti-IFN-ω or anti-IFN-α neutralizing antibodies did not induce $CD4^+$ T cell differentiation. The differentiated DCs were cultured with purified $CD4^+$ T cells at DC: $CD4^+$ T cells ratios of 1:20. Secreted IFN-γ was measured at day 6. Data is representative of 2 studies. Error bars indicate SD of Luminex triplicates. CONC: concentration.

[0015] FIG. **4**B shows secretion of IL-17 by $CD4^+$ T cells in the presence of DCs differentiated in the presence of IFN-ω, IFN-α, IFN-ω and anti -IFN-ω antibody, or IFN-α and anti-IFN-α antibody, or isotype control (iso) as indicated. DCs differentiated in the presence of either IFN-ω or IFN-α induced activation of $CD4^+$ T cells to a same degree, whereas DCs differentiated in the presence of anti-IFN-ω or anti-IFN-α neutralizing antibodies did not induce $CD4^+$ T cell differentiation. The differentiated DCs were cultured with purified $CD4^+$ T cells at DC: $CD4^+$ T cells ratios of 1:20. Secreted IL-17 was measured at day 6. Data is representative of 2 studies. Error bars indicate SD of Luminex triplicates. CONC: concentration.

[0016] FIG. **5**A shows that IFN-ω induces T-cell independent B cell activation to the same degree as IFN-α. B cell activation was assessed by CD86 surface expression using fluorescently labeled anti-CD86 antibody. T-cell independent B cell activation was induced by CpG (ODN2006) and/or anti-B cell receptor (aBCR) antibodies as indicated in the figure. IFN-ω or IFN-α (IFN-αB2) was used at indicated concentration. Median fluorescence was measured. B cells were obtained from one donor. The results were expressed as mean values of duplicate samples±SD.

[0017] FIG. **5**B shows that IFN-ω induces IL-6 secretion from B cells activated in non-T cell dependent fashion to the same degree as IFN-α. T-cell independent B cell activation was induced by CpG (ODN-2006) and/or anti-BCR antibodies (aBCR) as indicated in the figure. IFN-ω or IFN-α (IFN-α2B) was used at indicated concentration. IL-6 concentration is indicated as pg/ml. B cells were obtained from one donor. The results were expressed as mean values of duplicate samples±SD.

[0018] FIG. **6** shows that IFN-ω induces BLyS secretion from human PBMCs to the same degree as IFN-α (IFN-αB2). The concentration of IFN-ω or IFN-α used to stimulate PBMCs is indicated in the X-axis. BLyS concentration is shown as pg/ml. Results are expressed as mean values of duplicate samples±SD.

[0019] FIG. **7**A shows the overall molecular structure of the IFN-ω/Fab IFWM371 complex (only the Fv for the antibody is shown). The boxed area is magnified in FIG. **7**B. IFN-ω AB loop (AB), E helix (E) and D helix (D) of IFN-ω are indicated. Small circles represent water molecules. VL and VH or IFWM371 are indicated.

[0020] FIG. **7**B shows a magnification of the boxed area of FIG. **7**A, demonstrating hydrogen bonding network mediated through water molecules (water complex (WC) 1, 2, and 3) at the IFN-ω/Fab IFWM371interface. p FIG. **8**A shows the epitope in the IFN-ω/Fab IFWM371 complex. IFN-ω residue numbering according to SEQ ID NO: 1.

[0021] FIG. **8**B shows the paratope in the IFN-ω/Fab IFWM371 complex. Residues Y32, Y92, T94 and L96 are residues in the VL, and residues W33, 150, D57, T58, R59, H99, P100, G101, L102, N103,W104, A105 and D107 are residues in the VH in contact with IFN-ω. VL: SEQ ID NO: 29; VH: SEQ ID NO: 28. T94 and A105 are not shown in the figure.

[0022] FIG. **8**C shows a 2-dimensional interaction map between IFN-ω and Fab IFWM371. Boxed residues are VL paratope residues, and circled residues are VH paratope residues. Residues highlighted in gray are IFN-ω epitope residues. Numbering of VL, VH and IFN-ω residues is according to SEQ ID NOs: 29, 28 and 1, respectively. Van der Walls (VDW) and hydrophobic interactions are shown in solid lines, electrostatic and H bonds in dashed lines, arrows indicate backbone interactions with the arrows pointing to the backbone atoms. Most interactions are formed by the three IFN-ω epitope residues F27, L30 and R33.

[0023] FIG. **9** shows an alignment of IFN-ω with various IFN-α subtypes. Arrows indicate epitope residues IFWM371 binds to. F27, L30 and R33 are conserved across Type I IFNs, except in IFN-αD to which IFWM371 does not bind to. Residue numbering is according to human IFN-ω SEQ ID NO: 1 (IFNω-01 in the Figure). IFNα-01/D/1: SEQ ID NO: 18; IFNα-02/A: SEQ ID NO: 5; IFNα-04/a/b: SEQ ID NO: 15; IFNα-07/J: SEQ ID NO: 13; IFNα-10/C: SEQ ID NO: 7; IFNα-17/I: SEQ ID NO: 12 ; IFNα-21/F: SEQ ID NO: 9; IFNα-14/H: SEQ ID NO: 11; IFNα-16/WA: SEQ ID NO: 16; IFNα-08/B2: SEQ ID NO: 6; IFNα-05/G: SEQ ID NO: 10; IFNα-06/K: SEQ ID NO: 14.

[0024] FIG. **10** shows the IC_{50} values for select antibodies to various Type I IFNs in an ISRE assay.

[0025] FIG. **11**A shows neutralization of leukocyte IFN-induced IP 10 release in human whole blood with anti-IFN-

α/ω antibodies. Leukocyte IFN (Lk) was used to induce IP-10 secretion in healthy donor whole blood from 2 subjects. Whole blood was incubated with leukocyte interferon (LK) with or without anti-IFN-α/ω antibodies IFWM3522 or IFWM3525 at various concentrations (10 μg/ml-10 μg/ml) as indicated in the Figure. Bar represents mean and error bars SD from duplicate wells. Data is representative result of 2 independent experiments using whole blood from 2 different human donors.

[0026] FIG. **11**B shows neutralization of leukocyte IFN-induced IP-10 release in human whole blood with anti-IFN-α/ω antibodies. Leukocyte IFN (Lk) was used to induce IP-10 secretion in healthy donor whole blood from 2 subjects. Whole blood was incubated with leukocyte interferon (LK) with or without anti-IFN-α/ω antibody IFWM3399 or isotype control at various concentrations (10 μg/ml-10 μg/ml) as indicated in the Figure. Bar represents mean and error bars SD from duplicate wells. Data is representative result of 2 independent experiments using whole blood from 2 different human donors.

[0027] FIG. **12**A shows neutralization of SLE immune complex-induced IP-10 release in human whole blood with anti-IFN-α/ω antibodies. Whole blood was incubated with SLE immune complex-induced interferon preparations with or without anti-IFN-α/ω antibodies IFWM3522 or IFWM3525 at various concentrations (10 μg/ml-10 g/ml) as indicated in the Figure, and IP-10 was analyzed from plasma using an ELISA kit. Bar represents mean and error bars SD from duplicate wells. Data is representative result of 4 independent experiments using whole blood from 2 different human donors.

[0028] FIG. **12**B shows neutralization of SLE immune complex-induced IP-10 release in human whole blood with anti-IFN-α/ω antibodies. Whole blood was incubated with SLE immune complex-induced interferon preparations with or without anti-IFN-α/ω antibody IFWM3399 or isotype control at various concentrations (10 μg/ml-10 pg/ml) as indicated in the Figure, and IP-10 was analyzed from plasma using an ELISA kit. Bar represents mean and error bars SD from duplicate wells. Data is representative result of 4 independent experiments using whole blood from 2 different human donors.

[0029] FIG. **13**A shows normalization of MX1 gene expression in SLE patient blood after in vitro exposure of the blood to IFN-α/ω antibody IFWM2423 or isotype control for 24 hours at various concentrations (μg/ml) as indicated in the Figure. Bar represents mean and error bars SD from triplicate wells. MX1 gene expression was normalized to β-actin.

[0030] FIG. **13**B shows normalization of MX1 gene expression in SLE patient blood after in vitro exposure of the blood to IFN-α/ω antibody IFWM3522 and IFWM2525 or isotype control for 24 hours at various concentrations (μg/ml) as indicated in the Figure. Bar represents mean and error bars SD from triplicate wells. MX1 gene expression was normalized to β-actin.

[0031] FIG. **14**A shows the hydrogen (H) bond interactions between epitope residue R33 with VH of M371 as well as water molecules at the antibody/antigen interface in the IFN-ω/M341 structure.

[0032] FIG. **14**B shows modified H bond interactions between epitope residue R33 with VH of M3421 as well as water molecules in IFN-ω/M3421 structure.

[0033] FIG. **14**C shows the sequence (L96I mutation) and structural changes upon maturation of M371. In the M371 structure, F108 of VH is best described as having two alternative conformations. In the M3421 structure, they are converted into one conformation, suggesting tighter packing between VH and VL. In addition, there is a side chain rotamer flip of the W47 of VH.

[0034] FIG. **14**D shows sequence and structural changes upon M371 maturation. The VL Y32 was mutated into a more hydrophobic F (Y32F) and removing the two H bonds between Y32 in M371 and IFN-ω. VL A50 was mutated into F (A50F). This residue does not directly contact the antigen but stacks against W104 of VH that contacts the antigen. Two other changes (S31G and S30D) are not involved in antigen binding or directly impacting binding residues like A50F. These residue changes are likely to influence local hydrophobicity and optimize solvent interaction.

[0035] FIG. **15** shows s a 2-dimensional interaction map between IFN-ω and Fab IFWM3421. Boxed residues are VL paratope residues, and circled residues are VH paratope residues. Residues highlighted in gray are IFN-ω epitope residues. Numbering of VL, VH and IFN-ω residues is according to SEQ ID NOs: 28, 71 and 1, respectively. Van der Waals (VDW) and hydrophobic interactions are shown in solid lines, electrostatic and H bonds in dashed lines, arrows indicate backbone interactions with the arrows pointing to the backbone atoms. Most interactions are formed by the three IFN-ω epitope residues F27, L30 and R33.

[0036] FIG. **16** shows s a 2-dimensional interaction map between IFN-ω and Fab of IFWM3525. Boxed residues are VL paratope residues, and circled residues are VH paratope residues. Residues highlighted in gray are IFN-ω epitope residues. Numbering of VL, VH and IFN-ω residues is according to SEQ ID NOs: 28, 71 and 1, respectively. Van der Waals (VDW) and hydrophobic interactions are shown in solid lines, electrostatic and H bonds in dashed lines, arrows indicate backbone interactions with the arrows pointing to the backbone atoms. Most interactions are formed by the three IFN-ω epitope residues F27, L30 and R33.

SUMMARY OF THE INVENTION

[0037] One embodiment of the invention is an isolated monoclonal antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes.

[0038] Another embodiment of the invention is an isolated monoclonal antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes, wherein the antibody neutralizes the biological activity of the human IFN-ω with an IC_{50} of at least about 1×10^{-9}M or less, about 1×10^{-10} M or less, about 5×10^{11} M or less, or about 1×10^{-11}M or less.

[0039] In other embodiments, the antibody of the invention neutralizes the activity of at least three, four, five, six, seven, eight, nine, ten or eleven human IFN-α subtypes with an IC_{50} value of at least about 2×10^{-10} M or less, about 1.5×10^{-10} M or less, or about 1×10^{-10} M or less.

[0040] In other embodiments, the antibody comprises heavy chain complementarity determining region (HCDR) 1 (HCDR1), 2 (HCDR2) and 3 (HCDR3) amino acid sequences of SEQ ID NOs: 109, 114 and 121, respectfully, and light chain complementarity determining region (LCDR) 1 (LCDR1), 2 (LCDR2) and 3 (LCDR3) amino acid sequences of SEQ ID NOs: 118, 119 and 120.

[0041] In other embodiments, the antibody comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 114, 121, 159, 119 and 160, respectively.

[0042] In other embodiments, the antibody neutralizes at least ten human IFN-α subtypes selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJI, IFN-αK, IFN-αWA and IFN-α4a.

[0043] In other embodiments, the antibody binds human IFN-ω of SEQ ID NO: 1 at least at amino acid residues F27, L30 and R33.

[0044] In other embodiments, the antibody comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 114, 121, 161, 119 and 162, respectively.

[0045] In other embodiments, the antibody neutralizes at least the human IFN-α subtypes IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αJI and IFN-α4a.

[0046] In other embodiments, the antibody comprises a heavy chain variable region (VH) amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 150.

[0047] In other embodiments, the antibody comprises certain HCDR and LCDR sequences as described herein.

[0048] In other embodiments, the antibody comprises certain VH and VL sequences as described herein.

[0049] Another embodiment of the invention is a pharmaceutical composition comprising the antibody of the invention and a pharmaceutically accepted carrier.

[0050] Another embodiment of the invention is a polynucleotide encoding the antibody VH and/or the VL of the invention.

[0051] Another embodiment of the invention is a vector comprising the polynucleotide of the invention.

[0052] Another embodiment of the invention is a host cell comprising the vector of the invention.

[0053] Another embodiment of the invention is a method of producing the antibody of the invention, comprising culturing the host cell of the invention in conditions that the antibody is expressed, and recovering the antibody produced by the host cell.

[0054] Another embodiment of the invention is a method of treating an immune-mediated inflammatory disease or an autoimmune disease, comprising administering a therapeutically effective amount of an isolated antibody of the invention to a patient in need thereof for a time sufficient to treat or prevent the disease.

[0055] In some embodiments, the immune-mediated inflammatory disease or the autoimmune disease is lupus, psoriasis, immune thrombocytopenia (ITP), Aicardi-Goutieres syndrome (AGS), systemic sclerosis, Sjogren's syndrome, myositis, common variable immune deficiency (CVID), autoimmune thyroid disease, type I diabetes, rheumatoid arthritis, transplant rejection or graft versus host disease (GVHD).

DETAILED DESCRIPTION OF THE INVENTION

[0056] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

[0057] It is to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

[0058] Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, exemplary materials and methods are described herein. In describing and claiming the present invention, the following terminology will be used.

[0059] The term "specific binding" or "specifically binds" or "binds" as used herein refers to antibody binding to an antigen or an epitope within the antigen with greater affinity than for other antigens. Typically, the antibody binds to the antigen or the epitope within the antigen with a dissociation constant (K_D) of 1×10^{-8} M or less, for example 1×10^{-9} M or less, 1×10^{-10} M or less, 1×10^{-11} M or less, or 1×10^{-12} M or less, typically with a K_D that is at least ten fold less than its K_D for binding to a non-specific antigen (e.g., BSA, casein). The dissociation constant can be measured using standard procedures. Antibodies that specifically bind to the antigen or the epitope within the antigen may, however, have cross-reactivity to other related antigens, for example to the same antigen from other species (homologs), such as human or monkey, for example Macaca fascicularis (cynomolgus, cyno) or Pan troglodytes (chimpanzee, chimp) Antibodies that specifically bind to the antigen or the epitope within the antigen can further bind an epitope that is shared between two or more distinct antigens such as at least one interferon alpha (IFN-α) subtype and interferon omega (IFN-ω); i.e. antibodies cross-react with IFN-α subtypes and IFN-ω.

[0060] The term "neutralizing" or "neutralizes" or "neutralizing antibody" or "antibody antagonist" as used herein refers to an antibody or antibody fragment that partially or completely inhibits biological activity of recombinant human interferon omega (IFN-ω) and/or at least one recombinant human interferon alpha (IFN-α) subtype. Neutralizing antibodies may be identified using assays for IFN-α and/or IFN-ω biological activity as described herein. IFN-α and/or IFN-ω neutralizing antibody may inhibit measured IFN-α and/or IFN-ω biological activity by 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%.

[0061] The term "interferon-α" (IFN-α) as used herein refers to all native subtypes of human alpha interferons. Native IFN-α consists of at least 12 closely related protein subtypes encoded by distinct genes with a high degree of structural homology (Weissmann and Weber, Prog Nucl Acid Res Mol Biol., 33: 251, 1986; Roberts et al., J Interferon Cytokine Res. 18: 805-816, 1998). Nomenclature for human interferons is found at: http://www_genenames_org/genefamilies/_IFN. Table 4 shows the sequences of the IFN-α subtypes used herein, in addition to other Type I IFNs.

[0062] The term IFN-ω as used herein refers to human IFN-ω having the amino acid sequence shown in SEQ ID NO: 1 and UniProt accession number P05000. Human IFN-ω also includes the variant of SEQ ID NO: 2 having a threonine to glutamic acid substitution at position 80 (T80).

[0063] The term "type I interferon" or "IFN-I" refers to all native subtypes of human interferon-α and one subtype of interferon-β, interferon-ε, interferon-co and interferon-κ which bind to a common interferon receptor IFNAR.

[0064] As used herein the term "IFNAR" refers to the well-known interferon receptor which is a heterodimer or IFNAR1 and IFNAR2. IFNAR1 and IFNAR2 protein sequences are shown in SEQ ID NOs: 26 and 27, respectively. IFNAR1 mature extracellular domain spans residues 28-436 of SEQ ID NO: 26 and IFNAR2 mature extracellular domain spans residues 27-243 of SEQ ID NO: 27.

[0065] The term "antibodies" as used herein is meant in a broad sense and includes immunoglobulin molecules including polyclonal antibodies, monoclonal antibodies including murine, human, humanized and chimeric monoclonal antibodies, antibody fragments, bispecific or multispecific antibodies formed from at least two intact antibodies or antibody fragments, dimeric, tetrameric or multimeric antibodies, single chain antibodies, domain antibodies and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity.

[0066] Immunoglobulins can be assigned to five major classes, IgA, IgD, IgE, IgG and IgM, depending on the heavy chain constant domain amino acid sequence. IgA and IgG are further sub-classified as the isotypes IgA_1, IgA_2, IgG_1, IgG_2, IgG_3 and IgG_4. Antibody light chains of any vertebrate species can be assigned to one of two clearly distinct types, namely kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

[0067] The term "antibody fragments" refers to a portion of an immunoglobulin molecule that retains the heavy chain and/or the light chain antigen binding site, such as heavy chain complementarity determining regions (HCDR) 1, 2 and 3, light chain complementarity determining regions (LCDR) 1, 2 and 3, a heavy chain variable region (VH), or a light chain variable region (VL). Antibody fragments include well known Fab, F(ab')2, Fd and Fv fragments as well as domain antibodies (dAb) consisting one VH domain. VH and VL domains can be linked together via a synthetic linker to form various types of single chain antibody designs where the VH/VL domains pair intramolecularly, or intermolecularly in those cases when the VH and VL domains are expressed by separate single chain antibody constructs, to form a monovalent antigen binding site, such as single chain Fv (scFv) or diabody; described for example in Int. Pat. Publ. No. WO1998/44001, Int. Pat. Publ. No. WO1988/01649; Int. Pat. Publ. No. WO1994/13804; Int. Pat. Publ. No. WO1992/01047.

[0068] An antibody variable region consists of a "framework" region interrupted by three "antigen binding sites". The antigen binding sites are defined using various terms: (i) Complementarity Determining Regions (CDRs), three in the VH (HCDR1, HCDR2, HCDR3), and three in the VL (LCDR1, LCDR2, LCDR3), are based on sequence variability (Wu and Kabat, J Exp Med 132:211-50, 1970; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991). (ii) "Hypervariable regions", "HVR", or "HV", three in the VH (H1, H2, H3) and three in the VL (L1, L2, L3), refer to the regions of an antibody variable domains which are hypervariable in structure as defined by Chothia and Lesk (Chothia and Lesk, Mol Biol 196:901-17, 1987). Other terms include "IMGT-CDRs" (Lefranc et al., Dev Comparat Immunol 27:55-77, 2003) and "Specificity Determining Residue Usage" (SDRU) (Almagro, Mol Recognit 17:132-43, 2004). The International ImMunoGeneTics (IMGT) database (http://www_imgt_org) provides a standardized numbering and definition of antigen-binding sites. The correspondence between CDRs, HVs and IMGT delineations is described in Lefranc et al., Dev Comparat Immunol 27:55-77, 2003.

[0069] "Monoclonal antibody" as used herein refers to a homogenous antibody population with singular molecular composition. Monoclonal antibody may be nonspecific or multispecific.

[0070] "Chothia residues" as used herein are the antibody VL and VH residues numbered according to Al-Lazikani (Al-Lazikani et al., J Mol Biol 273:927-48, 1997).

[0071] "Framework" or "framework sequences" are the remaining sequences of a variable region other than those defined to be antigen binding site. Because the antigen binding site can be defined by various terms as described above, the exact amino acid sequence of a framework depends on how the antigen-binding site was defined.

[0072] "Humanized antibodies" refers to antibodies in which the antigen binding sites are derived from non-human species and the variable region frameworks are derived from human immunoglobulin sequences. Humanized antibodies may include substitutions in the framework regions so that the framework may not be an exact copy of expressed human immunoglobulin or germline gene sequences.

[0073] "Human-adapted" antibodies or "human framework adapted (HFA)" antibodies refers to humanized antibodies adapted according to methods described in U.S. Pat. Publ. No. US2009/0118127. Human-adapted antibodies are humanized by selecting the acceptor human frameworks based on the maximum CDR and FR similarities, length compatibilities and sequence similarities of CDR1 and CDR2 loops and a portion of light chain CDR3 loops.

[0074] "Human antibody" refers to an antibody having heavy and light chain variable regions in which both the framework and the antigen binding site regions are derived from sequences of human origin. If the antibody contains a constant region, the constant region also is derived from sequences of human origin.

[0075] Human antibody comprises heavy or light chain variable regions that are "derived from" sequences of human origin if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin or rearranged immunoglobulin genes. Such exemplary systems are human immunoglobulin gene libraries displayed on phage, and transgenic non-human animals such as mice carrying human immunoglobulin loci as described herein. "Human antibody" may contain amino acid differences when compared to the human germline or rearranged immunoglobulin sequences due to for example naturally occurring somatic mutations or intentional introduction of substitutions. Typically, "human antibody" is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% % identical in amino acid sequence to an amino acid sequence encoded by a human germline or rearranged immunoglobulin gene. In some cases, "human antibody" may contain consensus framework sequences derived from human framework sequence analyses, for example as described in Knappik et al (2000) *J. Mol. Biol.* 296:57-86), or synthetic HCDR3 incorporated into human immunoglobulin gene libraries displayed on phage, for example as described in Shi et al (2010) *J. Mol. Biol.* 397:385-96, 2010 and Int. Pat. Publ. No. WO2009/085462.

[0076] Isolated humanized antibodies are synthetic. Human antibodies, while derived from human immunoglobulin sequences, may be generated using systems such as phage display incorporating synthetic CDRs and/or synthetic frameworks, or can be subjected to in vitro mutagenesis to improve antibody properties, resulting in antibodies that do not naturally exist within the human antibody germline repertoire in vivo.

[0077] Human antibodies may include substitutions in the framework or in the antigen binding site so that they may not be exact copies of expressed human immunoglobulin or germline gene sequences. However, antibodies in which antigen binding sites are derived from a non-human species are not included in the definition of "human antibody".

[0078] The term "recombinant" as used herein, includes antibodies and other proteins, such as various IFN-α subtypes or IFN-ω that are prepared, expressed, created or isolated by recombinant means.

[0079] The term "epitope" as used herein means a portion of an antigen to which an antibody specifically binds. Epitopes usually consist of chemically active (such as polar, non-polar or hydrophobic) surface groupings of moieties such as amino acids or polysaccharide side chains and can have specific three-dimensional structural characteristics, as well as specific charge characteristics. An epitope can be composed of contiguous and/or discontiguous amino acids that form a conformational spatial unit. For a discontiguous epitope, amino acids from differing portions of the linear sequence of the antigen come in close proximity in 3-dimensional space through the folding of the protein molecule.

[0080] "Bispecific" as used herein refers to an antibody that binds two distinct antigens or two distinct epitopes within an antigen. The bispecific antibody may have cross-reactivity to other related antigens or can bind an epitope that is shared between two or more distinct antigens such as at least one IFN-α subtype and IFN-ω.

[0081] The term "in combination with" as used herein means that the drugs or therapeutics can be administered to an animal species such as human together in a mixture, concurrently as single agents or sequentially as single agents in any order.

[0082] The terms "IFN-α biological activity" and "IFN-ω biological activity" as used herein refer to any activity occurring as a result of IFN-α and IFN-ω, respectively, binding to its receptor IFNAR. One IFN-α and IFN-ω biological activity is the ability of IFN-α and IFN-ω to induce secreted embryonic alkaline phosphatase (SEAP) expression under the interferon inducible promoter such as ISG54 in HEK293 cells stably expressing signal transducer and activator of transcription 2 (STAT2), interferon regulatory factor 9 (IRF9) and SEAP using standard methods. Another IFN-α and IFN-ω biological activity is the induction of chemokine IP-10 (CXCL10) production from peripheral blood mononuclear cells (PBMCs) or whole blood as described herein.

[0083] The term "vector" means a polynucleotide capable of being duplicated within a biological system or that can be moved between such systems. Vector polynucleotides typically contain elements, such as origins of replication, polyadenylation signal or selection markers, that function to facilitate the duplication or maintenance of these polynucleotides in a biological system. Examples of such biological systems may include a cell, virus, animal, plant, and reconstituted biological systems utilizing biological components capable of duplicating a vector. The polynucleotide comprising a vector may be DNA or RNA molecules or a hybrid of these.

[0084] The term "expression vector" means a vector that can be utilized in a biological system or in a reconstituted biological system to direct the translation of a polypeptide encoded by a polynucleotide sequence present in the expression vector.

[0085] The term "polynucleotide" means a molecule comprising a chain of nucleotides covalently linked by a sugar-phosphate backbone or other equivalent covalent chemistry. Double and single-stranded DNAs and RNAs are typical examples of polynucleotides.

[0086] The term "polypeptide" or "protein" means a molecule that comprises at least two amino acid residues linked by a peptide bond to form a polypeptide. Small polypeptides of less than 50 amino acids may be referred to as "peptides".

[0087] Conventional one and three-letter amino acid codes are used herein as shown in Table 1.

TABLE 1

Amino acid	Three-letter code	One-letter code
Alanine	ala	A
Arginine	arg	R
Asparagine	asn	N
Aspartate	asp	D
Cysteine	cys	C
Glutamate	glu	E
Glutamine	gln	Q
Glycine	gly	G
Histidine	his	H
Isoleucine	ile	I
Leucine	leu	L
Lysine	lys	K
Methionine	met	M
Phenylalanine	phe	F
Proline	pro	P
Serine	ser	S
Threonine	thr	T
Tryptophan	trp	W
Tyrosine	tyr	Y
Valine	val	V

Compositions of Matter

[0088] The present invention provides monoclonal antibodies that bind to and neutralize activity of human interferon omega (IFN-ω) and multiple human interferon alpha (IFN-α) subtypes (anti-IFN-ζ/ω antibodies). The invention is based on, at least part, in the appreciation of the role of INF-ω in lupus pathogenesis with similar immunomodulatory effects than those of IFN-α alone. IFN-ω was found to be present and active in serum of lupus patients, and IFN-ω was found to induce similar cytokine release and gene expression profiles, dendritic cell differentiation, and T-cell independent B cell activation when compared to IFN-α; providing the basis for the rationale for neutralizing both IFN-α and IFN-ω to maximize therapeutic effect. The invention is also based, at least in part, on the identification of a minimal neutralizing epitope shared by IFN-ω and multiple IFN-α subtypes to which the IFN-α/ω antibodies of the invention bind. The IFN-α/ω antibodies of the invention may neutralize IFN-ω and multiple IFN-α subtypes with high efficacy, and thus they may be more potent in neutralizing SLE-relevant preparations of type I IFN and IFN signatures than antibodies neutralizing multiple IFN-α subtypes but not IFN-ω.

[0089] Therefore, the antibodies of the invention may be more efficacious in treating immune-mediated inflammatory diseases or autoimmune diseases including lupus. As the IFN-α/ω antibodies of the invention do not neutralize IFN-β, they may have more favorable safety and PK profiles when compared to the anti-IFNAR therapies, which are expected to block all type I IFNs.

[0090] One embodiment of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below is an isolated monoclonal antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes.

[0091] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes the activity of the human IFN-ω with an IC_{50} of at least about 1×10^{-9} M or less, about 1×10^{-10} M or less, about 5×10^{-11}M or less, or about 1×10^{-11}M or less, when the activity of the human IFN-α is the human IFN-ω-induced expression of secreted embryonic alkaline phosphatase (SEAP) under interferon inducible ISG54 promoter in HEK293 cells stably expressing signal transducer and activator of transcription 2 (STAT2), interferon regulatory factor 9 (IRF9) and SEAP ("ISRE assay" as described herein).

[0092] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJ1, IFN-αK, IFN-αWA and IFN-α4a.

[0093] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αH2 and IFN-αK.

[0094] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αG, IFN-αH2 and IFN-αK.

[0095] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αF, IFN-αG, IFN-αH2 and IFN-αK.

[0096] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αF, IFN-αG, IFN-αH2 and IFN-αK.

[0097] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αF, IFN-αG, IFN-αH2, IFN-αJ1 and IFN-αK.

[0098] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αG, IFN-αH2 and IFN-αK.

[0099] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αF, IFN-αG, IFN-αH2 and IFN-αK.

[0100] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αC, IFN-αG, IFN-αH2 and IFN-αK.

[0101] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αC, IFN-αF, IFN-αG and IFN-α4a.

[0102] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αF, IFN-αG, IFN-αH2, IFN-αI and IFN-αK.

[0103] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αF, IFN-αG, IFN-αH2, IFN-αJ1 and IFN-αK.

[0104] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αJI and IFN-αK.

[0105] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJl, IFN-αK and IFN-α4a.

[0106] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJl, IFN-αWA and IFN-α4a.

[0107] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αK, IFN-αWA and IFN-α4a.

[0108] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes IFN-ω and IFN-αA, IFN-αB, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJl, IFN-αK, IFN-αWA and IFN-α4a.

[0109] Antibodies of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may bind and neutralize at least three, four, five, six, seven, eight, nine, ten or eleven IFN-α subtypes in addition to neutralizing IFN-ω. The IFN-α subtypes and IFN-ω may be produced by recombinant expression using standard methods. Exemplary signal sequences that can be used for directing secretion are shown in SEQ ID NOs: 21-25.

[0110] The antibodies of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be tested for their ability to neutralize IFN-α and IFN-ω in a reporter gene assay using cell lines expressing reporter genes under an interferon responsive promoter, and stimulating cells with various

IFN-α subtypes and/or IFN-ω. For example, HEK-Blue™ IFN-α/β cells (InvivoGen, San Diego, Calif.) engineered to express a fully active type I IFN signaling pathway (stably expressing STAT2 and IRF9) and transfected with a SEAP reporter gene under the control of the IFNα/β inducible ISG54 promoter can be used as described herein. Signal from the alkaline phosphatase may be detected an IC_{50} may be calculated for the inhibition using well known methods.

[0111] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibodies of the invention neutralize the biological activity of the human IFN-ω with an IC_{50} value of about 1×10^{-9} M or less, about 1×10^{-10} M or less, about 5×10^{-11} M or less, or about 1×10^{-11} M or less, when the biological activity of the human IFN-ω is inhibition of secreted embryonic alkaline phosphatase (SEAP) expression under the interferon inducible ISG54 promoter in HEK293 cells stably expressing signal transducer and activator of transcription 2 (STAT2), interferon regulatory factor 9 (IRF9) and SEAP, using the assay "ISRE reporter gene assay" as described herein in Example 1.

[0112] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibodies of the invention neutralize the biological activity of the human IFN-ω with an IC_{50} value of at least about 1×10^{-10} M or less, when the IC_{50} is measured in the "ISRE reporter gene assay" described herein.

[0113] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibodies of the invention neutralize the biological activity of the human IFN-ω with an IC_{50} value between about 1×10^{-10} M to about 6×10^{-12} M, when the IC_{50} is measured in the "ISRE reporter gene assay" described herein. Skilled in the art will appreciate that the assay deviation for the ISRE reporter gene assay may typically be approximately within pIC_{50} of about 0.28 (log (M)). Therefore the term "about" reflects the typical standard deviation in the assay. For example, the typical SD for an IC_{50} of 1×10^{-9} M is between about 0.53×10^{-9} to 1.9×10^{-9}.

[0114] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibodies of the invention neutralize the biological activity at least three, four, five, six, seven, eight, nine, ten or eleven human IFN-α subtypes with an IC_{50} value of at least about 2×10^{-10} M or less, about 1.5×10^{-10} M or less, or about 1×10^{-10} M or less.

[0115] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes the activity of the human IFN-ω with an IC_{50} value of at least about 1×10^{-10} M or less, and at least 6 human IFN-α subtypes with an IC_{50} value of about 2×10^{-10} M or less, about 1.5×10^{-10} M or less, or about 1×10^{-10} M or less, when the IC_{50} value is measured using the "ISRE reporter gene assay" described herein.

[0116] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes the activity of the human IFN-ω with an IC_{50} value of at least about 1×10^{-10} M or less, and at least 10 human IFN-α subtypes with an IC_{50} value of about 2×10^{-10} M or less, about 1.5×10^{-10} M or less, or about 1×10^{-10} M or less, when the IC_{50} value is measured using the "ISRE reporter gene assay" described herein.

[0117] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes the activity of the human IFN-ω with an IC_{50} value of at least about 1×10^{-10} M or less, and at least 6 human IFN-α subtypes with an IC_{50} value of about 1×10^{-10} M or less, when the IC_{50} value is measured using the "ISRE reporter gene assay" described herein.

[0118] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes the activity of the human IFN-ω with an IC_{50} value of at least about 1×10^{-10} M or less, and at least 10 human IFN-α subtypes with an IC_{50} value of about 1×10^{-10} M or less, when the IC_{50} value is measured using the "ISRE reporter gene assay" described herein.

[0119] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibodies of the invention inhibit leukocyte interferon-induced IP-10 release in whole blood induced by 250 U/ml of interferon by about 50% or more in the presence of 10 μg/ml antibody than in the absence of the antibody.

[0120] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibodies of the invention inhibit systemic lupus erythematosus (SLE) immune complex-induced IP-10 release in whole blood by about 50% or more in the presence of 10 μg/ml antibody than in the absence of the antibody.

[0121] Antibodies of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, can be tested for their neutralizing ability by assessing their ability to inhibit IFN-induced cytokine release, such as IP-10 release from IFN-induced peripheral blood mononuclear cells (PBMCs) or whole blood. For example, PBMCs are isolated from heparinized whole blood from healthy volunteers using standard protocols, treated with a preformed complex of IFN and antibody to be tested, and IP-10 release is measured using standard methods such as Milliplex cytokine/chemokine kit (Millipore, Premixed 39 plex). Antibodies of the invention may inhibit IP-10 release by at least 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% when compared to IFN-induced IP-10 release in the absence of the antibody.

[0122] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibodies of the invention bind human IFN-ω with a dissociation constant (K_D) of about 1×10^{-10} M or less, about 5×10^{-11} M or less, about 1×10^{-11} M or less or about 5×10^{-12} M or less.

[0123] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention binds IFN-ω and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJ1, IFN-αK, IFN-αWA and IFN-α4a with a K_D of about 5×10^{-10} M or less, about 1×10^{-10} M or less, about 5×10^{-11} M or less, about 1×10^{-11} M or less, or about 5×10^{-12} M or less.

[0124] The affinity of an antibody to IFN-ω or to various IFN-α subtypes may be determined experimentally using any suitable method. Such methods may utilize ProteOn XPR36,

Biacore 3000 or KinExA instrumentation, ELISA or competitive binding assays known to those skilled in the art. The measured affinity of a particular antibody/IFN-ω or antibody/IFN-α subtypes interaction may vary if measured under different conditions (e.g., osmolarity, pH). Thus, measurements of affinity and other binding parameters (e.g., K_D, K_{on}, K_{off}) are preferably made with standardized conditions and a standardized buffer, such as the buffer described herein. Skilled in the art will appreciate that the internal error for affinity measurements for example using Biacore 3000 or ProteOn (measured as standard deviation, SD) can typically be within 5-33% for measurements within the typical limits of detection. Therefore the term "about" reflects the typical standard deviation in the assay. For example, the typical SD for a K_D of 1×10^{-9} M is up to $\pm0.33\times10^{-9}$M.

[0125] The antibodies binding human IFN-ω and IFN-α subtypes with a desired affinity and neutralization profile may be selected from libraries of variants or fragments by panning with human IFN-ω and/or IFN-α subtypes and optionally by further antibody affinity maturation. In an exemplary panning campaign, phage libraries may be panned sequentially or using a mixture of chimpanzee IFN-ω and human IFN-α subtypes IFN-α2, IFN-α1, IFN-αH2, IFN-αG and IFN-αF. Alternatively, antibodies of the invention may be generated by immunizing mice with chimpanzee and cynomolgus IFN-ω, human IFN-α subtypes IFN-αD, IFN-αJ1, IFN-αC, IFN-αB2, IFN-αH2, IFN-αA, IFN-α4a, IFN-αG, IFN-αF, IFN-αWA and IFN-αI, and screening the hybriomas for binding to IFN-ω and various IFN-α subtypes, and subsequently assessing the neutralization ability of the antibodies using methods described herein.

[0126] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises heavy chain complementarity determining region (HCDR) 1 (HCDR1), 2 (HCDR2) and 3 (HCDR3) amino acid sequences of SEQ ID NOs: 109, 114 and 121, respectfully, and light chain complementarity determining region (LCDR) 1 (LCDR1), 2 (LCDR2) and 3 (LCDR3) amino acid sequences of SEQ ID NOs: 118, 119 and 120.

[0127] Exemplary such antibodies are antibodies IFWM3308, IFWM3307, IFWM3410, IFWM3322, IFWM3385, IFWM3416, IFWM3310, IFWM3400, IFWM3321, IFWM3522, IFWM3524, IFWM3320, IFWM3304, IFWM3520, IFWM3399, IFWM3314, IFWM3331, IFWM3405, IFWM3442, IFWM3525, IFWM3423, IFWM3444 and IFWM3421. These antibodies neutralize human IFN-ω and at least three IFN-α subtypes with an IC_{50} value of about 1×10^{-10} M or less, and comprise a consensus LCDR1 (SEQ ID NO: 118), LCDR2 (SEQ ID NO: 119), LCDR3 (SEQ ID NO: 120), HCDR2 (SEQ ID NO: 114) and HCDR3 (SEQ ID NO: 121) amino acid sequences and a constant HCDR1 (SEQ ID NO: 109) amino acid sequence. Antibodies having substitutions at least at VH residue position 103 of SEQ ID NOs: 28, 31, 157 or 158, VL residue positions 30, 31, 32, 50, 91-94 or 96 of SEQ ID NOs: 35, 39, 40, 42, 46, 52, 53, 54, 71, 73, 75 or 135, and VL residues positions 30, 31, 32, 50, 51, 92-95 or 97 of SEQ ID NOs: 57, 61, 62, 68 and 150 resulted in antibodies having improved potency when compared to the parental IFWM371 antibody.

[0128] SEQ ID NO: 118
[0129] QSIX1X2X3X4; wherein
[0130] X_1 is G, D, A, R, E, S, or N;
[0131] X_2 is D, G, N, S, R, E or K;
[0132] X_3 is F, A, N, T, S or V;
[0133] X_4 is Y, N or deleted.
[0134] SEQ ID NO: 119
[0135] X_5AS; wherein
[0136] X_5 is F, W or G.
[0137] SEQ ID NO: 120
[0138] $QQX_6X_7X_8X_9PX_{10}T$; wherein
[0139] X_6 is A, G, S or W;
[0140] X_7 is L, Y, H, W, F or I;
[0141] X_8 is D or S;
[0142] X_9 is F, T, L, N or W; and
[0143] X_{10} is L, F or I.
[0144] SEQ ID NO: 114
[0145] $IX_{11}X_{12}SDSDT$; wherein
[0146] X_{11} is D or A; and
[0147] X_{12} is P or A.
[0148] SEQ ID NO: 121
[0149] $ARHPGLX_{13}WAPDFDY$; wherein
[0150] X_{13} is A or N.
[0151] SEQ ID NO: 109
[0152] GYSFTSYW
[0153] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, theHCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 114, 121, 159, 119 and 160, respectively.
[0154] Exemplary such antibodies are antibodies IFWM3400, IFWM3321, IFWM3522, IFWM3524, IFWM3320, IFWM3304, IFWM3520, IFWM3399, IFWM3314, IFWM3331, IFWM3405, IFWM3442, IFWM3525, IFWM3423, IFWM3444 and IFWM3421. These antibodies neutralize human IFN-ω and at least six IFN-α subtypes with an IC_{50} value of about 1×10^{-10} M or less, and comprise a consensus LCDR1 (SEQ ID NO: 159), LCDR2 (SEQ ID NO: 119), LCDR3 (SEQ ID NO: 160), HCDR2 (SEQ ID NO: 114) and HCDR3 (SEQ ID NO: 121) amino acid sequences and a constant HCDR1 (SEQ ID NO: 109) amino acid sequence.
[0155] SEQ ID NO: 159
[0156] QSIX14X15X16X17; wherein
[0157] X_{14} is G, D, A, E, S, or N;
[0158] X_{15} is D, G, N, S or R;
[0159] X_{16} is F, A, N, S or V; and
[0160] X_{17} is Y, N or deleted.
[0161] SEQ ID NO: 160
[0162] $QQX_{18}X_{19}X_{20}X_{21}PX_{22}T$; wherein
[0163] X_{18} is A, G or S;
[0164] X_{19} is Y, H, W or F;
[0165] X_{20} is D or S;
[0166] X_{21} is F, T, L or W; and
[0167] X_{22} is L, F or I.
[0168] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, theHCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 114, 121, 161, 119 and 162, respectively.
[0169] Exemplary such antibodies are antibodies IFWM3405, IFWM3442, IFWM3525, IFWM3423, IFWM3444 and IFWM3421. These antibodies neutralize human IFN-ω and at least ten IFN-α subtypes with an IC_{50} value of at least about 2×10^{-10} M or less, about 1.5×10^{-10} M

or less, or about 1×10^{-10} M or less, and comprise a consensus LCDR1 (SEQ ID NO: 161), LCDR2 (SEQ ID NO: 119), LCDR3 (SEQ ID NO: 162), HCDR2 (SEQ ID NO: 114) and HCDR3 (SEQ ID NO: 121) sequences and a constant HCDR1 (SEQ ID NO: 109) sequence.

[0170] SEQ ID NO: 161

[0171] $QSIX_{23}X_{24}X_{25}X_{26}$; wherein

[0172] X_{23} is A or D;

[0173] X_{24} is N or G;

[0174] X_{25} is F, N or S; and

[0175] X_{26} is Y, N or deleted.

[0176] SEQ ID NO: 162

[0177] $QQX_{27}X_{28}X_{29}X_{30}PX_{31}T$; wherein

[0178] X_{27} is G or S;

[0179] X_{28} is Y;

[0180] X_{29} is D;

[0181] X_{30} is F, T or L; and

[0182] X_{31} is L, F or I.

[0183] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention neutralizes human IFN-ω and at least ten human IFN-α subtypes selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJ1, IFN-αK, IFN-αWA and IFN-α4a.

[0184] In some embodiments of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody neutralizes human IFN-ω and at least the human IFN-α subtypes IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αJl and IFN-α4a.

[0185] In some embodiments of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody does not bind or neutralize IFN-αD or IFN-α1.

[0186] In some embodiments of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody does not bind or neutralize IFN-β.

[0187] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises

[0188] the HCDR1 amino acid sequence of SEQ ID NO: 109;

[0189] the HCDR2 amino acid sequence of SEQ ID NOs: 111, 112 or 113;

[0190] the HCDR3 amino acid sequence of SEQ ID NOs: 115 or 116;

[0191] the LCDR1 amino acid sequence of SEQ ID NOs: 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91;

[0192] the LCDR2 amino acid sequence of SEQ ID NOs: 93, 94 or 95; and

[0193] the LCDR3 amino acid sequence of SEQ ID NOs: 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106 or 107.

[0194] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs:

[0195] a) 109, 113, 116, 77, 93 and 104, respectively;

[0196] b) 109, 113, 116, 85, 93 and 96, respectively;

[0197] c) 109, 113, 115, 79, 95 and 107, respectively;

[0198] d) 109, 113, 116, 76, 93 and 103, respectively;

[0199] e) 109, 113, 115, 85, 93 and 96, respectively;

[0200] f) 109, 113, 115, 89, 95 and 100, respectively;

[0201] g) 109, 113, 116, 86, 93 and 105, respectively;

[0202] h) 109, 113, 115, 76, 93 and 103, respectively;

[0203] i) 109, 113, 116, 80, 93 and 97, respectively;

[0204] j) 109, 113, 116, 84, 93 and 97, respectively;

[0205] k) 109, 113, 116, 90, 93 and 97, respectively;

[0206] l) 109, 113, 116, 88, 93 and 102, respectively;

[0207] m) 109, 113, 116, 87, 93 and 105, respectively;

[0208] n) 109, 113, 116, 91, 93 and 106, respectively;

[0209] o) 109, 113, 115, 80, 93 and 97, respectively;

[0210] p) 109, 113, 116, 83, 93 and 101, respectively;

[0211] q) 109, 113, 116, 82, 94 and 98, respectively;

[0212] r) 109, 113, 115, 78, 95 and 100, respectively;

[0213] s) 109, 111, 116, 81, 93 and 106, respectively;

[0214] t) 109, 113, 116, 82, 94 and 99, respectively;

[0215] u) 109, 113, 115, 81, 93 and 106, respectively;

[0216] v) 109, 112, 116, 81, 93 and 106, respectively; or

[0217] w) 109, 113, 116, 81, 93 and 106, respectively.

[0218] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 77, 93 and 104, respectively.

[0219] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 85, 93 and 96, respectively.

[0220] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 115, 79, 95 and 107, respectively.

[0221] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 76, 93 and 103, respectively.

[0222] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 115, 85, 93 and 96, respectively.

[0223] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 115, 89, 95 and 100, respectively.

[0224] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 86, 93 and 105, respectively.

[0225] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodi-

ments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 115, 76, 93 and 103, respectively.

[0226] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 80, 93 and 97, respectively.

[0227] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 84, 93 and 97, respectively.

[0228] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 90, 93 and 97, respectively.

[0229] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 88, 93 and 102, respectively.

[0230] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 87, 93 and 105, respectively.

[0231] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 91, 93 and 106, respectively.

[0232] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 115, 80, 93 and 97, respectively.

[0233] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 83, 93 and 101, respectively.

[0234] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 82, 94 and 98, respectively.

[0235] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 115, 78, 95 and 100, respectively.

[0236] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 111, 116, 81, 93 and 106, respectively.

[0237] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 82, 94 and 99, respectively.

[0238] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 115, 81, 93 and 106, respectively.

[0239] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 112, 116, 81, 93 and 106, respectively.

[0240] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 113, 116, 81, 93 and 106, respectively.

[0241] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody comprises the VH and the VL wherein the VH comprises the amino acid sequence of SEQ ID NOs: 28, 31, 157 or 158.

[0242] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody comprises the VH and the VL, wherein the VL comprises the amino acid sequence of SEQ ID NOs: 35, 39, 40, 42, 46, 52, 53, 54, 57, 61, 62, 68, 71, 73, 75, 135 or 150.

[0243] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody comprises the VH of SEQ ID NOs: 28, 31, 157 or 158, and the VL of SEQ ID NOs: 35, 39, 40, 42, 46, 52, 53, 54, 57, 61, 62, 68, 71, 73, 75, 135 or 150.

[0244] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH and the VL of SEQ ID NOs: 28 and 40, 28 and 39, 31 and 62, 28 and 54, 31 and 39, 31 and 68, 28 and 42, 31 and 54, 28 and 53, 28 and 73, 28 and 75, 28 and 52, 28 and 35, 28 and 135, 31 and 53, 28 and 46, 28 and 61, 31 and 57, 157 and 71, 28 and 150, 31 and 71, 158 and 71, or 28 and 71.

[0245] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody comprises the VH and the VL, wherein the VH comprises the amino acid sequence of SEQ ID NOs: 28, 30, 31, 157 or 158.

[0246] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of the VH of SEQ ID NOs: 28, 30, 31, 157 or 158, and the LCDR1, LCDR2 and

LCDR3 amino acid sequences of the VL of SEQ ID NOs: 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 74, 148, 149, 150, 151, 152 or 153, wherein the CDRs are defined according to Kabat, Chothia and/or IMGT.

[0247] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody comprises the VH and the VL, wherein the VL comprises the amino acid sequence of SEQ ID NOs: 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 74, 148, 149, 150, 151, 152 or 153.

[0248] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody comprises the VH and the VL, wherein the VH comprises the amino acid sequence of SEQ ID NOs: 28, 30, 31, 157 or 158, and the VL comprises the amino acid sequence of SEQ ID NOs: 29, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 73, 74, 75, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 74, 148, 149, 150, 151, 152 or 153.

[0249] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 29.

[0250] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 32.

[0251] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 33.

[0252] In some embodiment described herein, and in some embodiments of each and every one of the numbered embodiments listed below s, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 34.

[0253] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 35.

[0254] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 36.

[0255] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 37.

[0256] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 38.

[0257] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 39.

[0258] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 40.

[0259] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 41.

[0260] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 42.

[0261] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 43.

[0262] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 44.

[0263] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 45.

[0264] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 46.

[0265] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 47.

[0266] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 48.

[0267] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 49.

[0268] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 50.

[0269] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 51.

[0270] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 52.

[0271] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 53.

[0272] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 54.

[0273] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodi-

ments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 55.

[0274] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 56.

[0275] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 57.

[0276] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 58.

[0277] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 59.

[0278] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 60.

[0279] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 61.

[0280] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 62.

[0281] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 63.

[0282] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 64.

[0283] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 65.

[0284] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 66.

[0285] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 67.

[0286] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 68.

[0287] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 69.

[0288] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 32.

[0289] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 33.

[0290] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 34.

[0291] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 35.

[0292] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 36.

[0293] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 37.

[0294] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 38.

[0295] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 39.

[0296] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 40.

[0297] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 41.

[0298] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 42.

[0299] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 43.

[0300] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 44.

[0301] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 45.

[0302] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 46.

[0303] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 47.

[0304] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 48.

[0305] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodi-

ments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 49.

[0306] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 50.

[0307] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 51.

[0308] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 52.

[0309] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 53.

[0310] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 54.

[0311] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 56.

[0312] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 57.

[0313] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 58.

[0314] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 59.

[0315] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 60.

[0316] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 61.

[0317] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 62.

[0318] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 63.

[0319] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 64.

[0320] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 65.

[0321] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 66.

[0322] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 67.

[0323] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 68.

[0324] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 69.

[0325] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 32.

[0326] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 33.

[0327] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 34.

[0328] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 35.

[0329] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 36.

[0330] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 37.

[0331] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 38.

[0332] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 39.

[0333] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 40.

[0334] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 41.

[0335] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 42.

[0336] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 43.

[0337] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodi-

ments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 44.

[0338] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 45.

[0339] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 46.

[0340] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 47.

[0341] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 48.

[0342] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 49.

[0343] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 50.

[0344] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 51.

[0345] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 52.

[0346] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 53.

[0347] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 54.

[0348] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 56.

[0349] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 57.

[0350] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 58.

[0351] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 59.

[0352] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 60.

[0353] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 61.

[0354] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 62.

[0355] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 63.

[0356] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 65.

[0357] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 66.

[0358] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 67.

[0359] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 68.

[0360] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 69.

[0361] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 70.

[0362] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 70.

[0363] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 30 and the VL of SEQ ID NO: 70.

[0364] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 71.

[0365] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 31 and the VL of SEQ ID NO: 71.

[0366] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 123.

[0367] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 124.

[0368] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 125.

[0369] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodi-

ments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 126.

[0370] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 127.

[0371] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 128.

[0372] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 129.

[0373] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 130.

[0374] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 131.

[0375] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 132.

[0376] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 133.

[0377] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 134.

[0378] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 135.

[0379] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 136.

[0380] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 137.

[0381] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 138.

[0382] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 139.

[0383] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 140.

[0384] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 141.

[0385] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 73.

[0386] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 142.

[0387] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 143.

[0388] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 74.

[0389] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 75.

[0390] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 144.

[0391] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 145.

[0392] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 146.

[0393] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 147.

[0394] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 148.

[0395] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 149.

[0396] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 150.

[0397] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 151.

[0398] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 152.

[0399] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 153.

[0400] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 157 and the VL of SEQ ID NO: 71.

[0401] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodi-

ments listed below, the antibody of the invention comprises the VH of SEQ ID NO: 158 and the VL of SEQ ID NO: 71.

[0402] Variants of the anti-IFN-ω/α antibodies of the invention comprising VH or VL amino acid sequences shown in Table 9, Table 13, Table 15, Table 17, Table 19 and Table 21 are within the scope of the invention. For example, variants may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 amino acid substitutions in the VH and/or VL that do not adversely affect the antibody properties. In some embodiments, the sequence identity may be about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% to a VH or the VL amino acid sequence of the invention. Percent identity can be determined for example by pairwise alignment using the default settings of the AlignX module of Vector NTI v.9.0.0 (Invitrogen, Carslbad, Calif.). Exemplary modifications are for example conservative amino acid substitutions in the antigen-binding site or in the framework without adversely altering the properties of the antibody. Conservative substitutions may also be made to improve antibody properties, for example stability or affinity. Conservative substitutions are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids can be divided into four families: (1) acidic (aspartate, glutamate); (2) basic (lysine, arginine, histidine); (3) nonpolar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan); and (4) uncharged polar (glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine). Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids. Alternatively, the amino acid repertoire can be grouped as (1) acidic (aspartate, glutamate); (2) basic (lysine, arginine histidine), (3) aliphatic (glycine, alanine, valine, leucine, isoleucine, serine, threonine), with serine and threonine optionally be grouped separately as aliphatic-hydroxyl; (4) aromatic (phenylalanine, tyrosine, tryptophan); (5) amide (asparagine, glutamine); and (6) sulfur-containing (cysteine and methionine) (Stryer (ed.), Biochemistry, 2nd ed, WH Freeman and Co., 1981). Furthermore, any native residue in the polypeptide may also be substituted with alanine, as has been previously described for alanine scanning mutagenesis (MacLennan et al (1998) *Acta Physiol. Scand. Suppl.* 643:55-67; Sasaki et al (1998) *Adv. Biophys.* 35:1-24). Desired amino acid substitutions may be determined by those skilled in the art at the time such substitutions are desired. The resulting antibody variants may be tested for their characteristics using assays described herein.

[0403] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-IFN-α/ω antibody of the invention comprises a heavy chain variable region (VH) amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 71.

[0404] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-IFN-α/ω antibody of the invention comprises a heavy chain variable region (VH) amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 150.

[0405] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-IFN-α/ω antibody of the invention comprises a heavy chain variable region (VH) amino acid sequence at least 95% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 95% identical to SEQ ID NO: 71.

[0406] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-IFN-α/ω antibody of the invention comprises a heavy chain variable region (VH) amino acid sequence at least 95% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 95% identical to SEQ ID NO: 150.

[0407] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-IFN-α/ω antibody of the invention comprises a heavy chain variable region (VH) amino acid sequence at least 97% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 97% identical to SEQ ID NO: 71.

[0408] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the anti-IFN-α/ω antibody of the invention comprises a heavy chain variable region (VH) amino acid sequence at least 97% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 97% identical to SEQ ID NO: 150.

[0409] Amino acid substitutions may be done for example by PCR mutagenesis (US Pat. No. 4,683,195). Alternatively, libraries of variants may be generated using known methods, for example using random (NNK) or non-random codons, for example DVK codons, which encode 11 amino acids (Ala, Cys, Asp, Glu, Gly, Lys, Asn, Arg, Ser, Tyr, Trp) and screening the libraries for variants with desired properties.

[0410] Although the embodiments illustrated in the Examples comprise pairs of variable regions, one from a heavy chain and one from a light chain, a skilled artisan will recognize that alternative embodiments may comprise single heavy or light chain variable regions. The single variable region can be used to screen for variable domains capable of forming a two-domain specific antigen-binding fragment capable of, for example, binding to human IFN-ω or various human IFN-α subtypes. The screening may be accomplished by phage display screening methods using for example hierarchical dual combinatorial approach disclosed in Int. Pat. Publ. No. WO92/01047. In this approach, an individual colony containing either a H or L chain clone is used to infect a complete library of clones encoding the other chain (L or H), and the resulting two-chain specific antigen-binding domain is selected in accordance with phage display techniques as described. Therefore, the individual VH and VL polypeptide chains are useful in identifying additional antibodies specifically binding to human IFN-ω or various IFN-α subtypes using the methods disclosed in Int. Pat. Publ. No. WO92/01047.

[0411] Antibodies of the invention may be made using a variety of technologies for generating antibodies. For example, the hybridoma method of Kohler and Milstein, *Nature* 256:495, 1975 may be used to generate monoclonal antibodies. In the hybridoma method, a mouse or other host animal, such as a hamster, rat or monkey, is immunized with human IFN-ω and/or various IFN-α subtypes or fragments of these proteins, followed by fusion of spleen cells from immu-

nized animals with myeloma cells using standard methods to form hybridoma cells (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Colonies arising from single immortalized hybridoma cells are screened for production of antibodies with desired properties, such as specificity of binding, cross-reactivity or lack thereof, and affinity for the antigen.

[0412] Various host animals may be used to produce the IFN-α/ω antibodies of the invention. For example, Balb/c mice may be used to generate mouse anti-human IFN-α/ω antibodies. The antibodies made in Balb/c mice and other non-human animals may be humanized using various technologies to generate more human-like sequences. Exemplary humanization techniques including selection of human acceptor frameworks are known to skilled in the art and include CDR grafting (U.S. Pat. No. 5,225,539), SDR grafting (U.S. Pat. No. 6,818,749), Resurfacing (Padlan, Mol Immunol 28:489-499, 1991), Specificity Determining Residues Resurfacing (U.S. Pat. Publ. No. 20100261620), human-adaptation (or human framework adaptation) (U.S. Pat. Publ. No. US2009/0118127), Superhumanization (U.S. Pat. No. 7,709, 226) and guided selection (Osbourn et al (2005) Methods 36:61-68, 2005; U.S. Pat. No. 5,565,332).

[0413] Humanized antibodies may be further optimized to improve their selectivity or affinity to a desired antigen by incorporating altered framework support residues to preserve binding affinity (backmutations) by techniques such as those disclosed as described in Int. Pat. Publ. No. WO90/007861 and in Int. Pat. Publ. No. WO92/22653.

[0414] Transgenic mice carrying human immunoglobulin (Ig) loci in their genome may be used to generate human antibodies against a target protein, and are described in for example Int. Pat. Publ. No. WO90/04036, U.S. Pat. No. 6150584, Int. Pat. Publ. No. WO99/45962, Int. Pat. Publ. No. WO02/066630, Int. Pat. Publ. No. WO02/43478, Lonberg et al (1994) *Nature* 368:856-9; Green et al (1994) *Nature Genet.* 7:13-21; Green & Jakobovits (1998) *Exp. Med.* 188:483-95; Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93; Bruggemann et al (1991) *Eur. J. Immunol.* 21:1323- 1326; Fishwild et al (1996) *Nat. Biotechnol.* 14:845-851; Mendez et al (1997) *Nat. Genet.* 15:146-156; Green (1999)*J. Immunol. Methods* 231:11-23; Yang et al (1999) *Cancer Res.* 59:1236-1243; Brüggemann and Taussig (1997) *Curr. Opin. Biotechnol.* 8:455-458; Int. Pat. Publ. No. WO02/043478). The endogenous immunoglobulin loci in such mice may be disrupted or deleted, and at least one complete or partial human immunoglobulin locus may be inserted into the mouse genome using homologous or non-homologous recombination, using transchromosomes, or using minigenes. Companies such as Regeneron (http://_wwwregeneron_com), Harbour Antibodies (http://_www_harbourantibodies_com), Open Monoclonal Technology, Inc. (OMT) (http://_www_omtinc_net), KyMab (http://_www_kymab_com), Trianni (http://_www.trianni_com) and Ablexis (http://_www_ablexis_com) can be engaged to provide human antibodies directed against a selected antigen using technology as described above.

[0415] Human antibodies may be selected from a phage display library, where the phage is engineered to express human immunoglobulins or portions thereof such as Fabs, single chain antibodies (scFv), or unpaired or paired antibody variable regions (Knappik et al (2000) *J. Mol. Biol.* 296:57-86; Krebs et al (2001) *J. Immunol. Meth.* 254:67-84; Vaughan et al (1996) *Nature Biotechnology* 14:309-314; Sheets et al (1998) *PITAS* (USA) 95:6157-6162; Hoogenboom and Winter, (1991) *J. Mol. Biol.* 227:381; Marks et al (1991) *J. Mol. Biol.* 222:581). The antibodies of the invention may be isolated for example from phage display library expressing antibody heavy and light chain variable regions as fusion proteins with bacteriophage pIX coat protein as described in Shi et al (2010)*J. Mol. Biol.* 397:385-96 and Int. Pat. Publ. No. WO09/085462). The libraries may be screened for phage binding to human IFN-ω and IFN-α and the obtained positive clones may be further characterized, the Fabs isolated from the clone lysates, and expressed as full length IgGs. Such phage display methods for isolating human antibodies are described in for example: U.S. Pat. Nos. 5,223,409; 5,403,484; and 5,571,698 to Ladner et al.; U.S. Pat. Nos. 5,427,908 and 5, 580,717 to Dower et al.; U.S. Pat. Nos. 5,969,108 and 6,172,197 to McCafferty et al.; and U.S. Pat. Nos. 5,885,793; 6,521,404; 6,544,731; 6,555,313; 6,582,915 and 6,593,081 to Griffiths et al.

[0416] Preparation of immunogenic antigens and monoclonal antibody production may be performed using any suitable technique, such as recombinant protein production. The immunogenic antigens may be administered to an animal in the form of purified protein, or protein mixtures including whole cells or cell or tissue extracts, or the antigen may be formed de novo in the animal's body from nucleic acids encoding said antigen or a portion thereof.

[0417] In an exemplary method, phage display libraries may be panned against biotinylated human IFN-α2 or biotinylated human IFN-αG. After three rounds of panning, a polyclonal phage ELISA using human IFN-α2, IFN-αG and IFN-ω as antigens may be performed to detect the specific enrichment of individual panning experiments. The phage demonstrating enrichment for binders to IFN-α2, IFN-αG and IFN-ω may be collected and further screened in a standard ELISA assay for binding to additional IFN-α subtypes in Fab format. The identified Fab clones may be cloned to full length antibodies and characterized further for their affinity and neutralization ability of human IFN-ω and various IFN-α subtypes using ProteOn and ISRE reporter gene assay as described herein.

[0418] The antibodies of the invention may be human or humanized.

[0419] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the IFN-α/ω antibodies of the invention comprise a VH framework derived from human germline gene IGHV5-51 (SEQ ID NO: 155).

[0420] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the IFN-α/ω antibodies of the invention comprise a VL framework derived from human germline gene IGKV1D-39 (SEQ ID NO: 156).

[0421] The antibodies of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be of IgA, IgD, IgE, IgG or IgM type. The antibodies of the invention may be of IgG1, IgG2, IgG3, IgG4 type.

[0422] Immune effector properties of the antibodies of the invention may be enhanced or silenced through Fc modifications by techniques known to those skilled in the art. For example, Fc effector functions such as Clq binding, complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), phagocytosis, down regulation of cell surface receptors (e.g., B cell receptor;

BCR), etc. can be provided and/or controlled by modifying residues in the Fc responsible for these activities. Pharmacokinetic properties of the antibodies of the invention may be enhanced by mutating residues in the Fc domain that extend antibody half-life (Strohl (2009) Curr Opin Biotechnol 20:685-91). Exemplary Fc modifications are IgG4 S228P/L234A/L235A, IgG2 M252Y/S254T/T256E (Dall'Acqua et al (2006) *J. Biol. Chem.* 281:23514-24; or IgG2 V234A/G237A/P238S, V234A/G237A/H268Q, H268AN309L/A330S/P331 or V234A/G237A/P238S/H268AN309L/A330S/P331S on IgG2 (Intl. Pat. Publ. No. WO11/066501), of those described in US. Pat. No. 6,737,056 (residue numbering according to the EU numbering).

[0423] Additionally, antibodies of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be post-translationally modified by processes such as glycosylation, isomerization, deglycosylation or non-naturally occurring covalent modification such as the addition of polyethylene glycol moieties (pegylation) and lipidation. Such modifications may occur in vivo or in vitro. For example, the antibodies of the invention may be conjugated to polyethylene glycol (PEGylated) to improve their pharmacokinetic profiles. Conjugation may be carried out by techniques known to those skilled in the art. Conjugation of therapeutic antibodies with PEG has been shown to enhance pharmacodynamics while not interfering with function (Knigh et al (2004) *Platelets* 15:409-18; Leong et al (2001) *Cytokine* 16:106-19; Yang et al (2003) *Protein Eng.* 16:761-70).

[0424] Antibodies or fragments thereof of the invention modified to improve stability, selectivity, cross-reactivity, affinity, immunogenicity or other desirable biological or biophysical property are within the scope of the invention. Stability of an antibody is influenced by a number of factors, including (1) core packing of individual domains that affects their intrinsic stability, (2) protein/protein interface interactions that have impact upon the HC and LC pairing, (3) burial of polar and charged residues, (4) H-bonding network for polar and charged residues; and (5) surface charge and polar residue distribution among other intra- and inter-molecular forces (Worn et al (2001) *J. Mol. Biol.* 305:989-1010). Potential structure destabilizing residues may be identified based upon the crystal structure of the antibody or by molecular modeling in certain cases, and the effect of the residues on antibody stability can be tested by generating and evaluating variants harboring mutations in the identified residues. One of the ways to increase antibody stability is to raise the thermal transition midpoint (T_m) as measured by differential scanning calorimetry (DSC). In general, the protein T_m is correlated with its stability and inversely correlated with its susceptibility to unfolding and denaturation in solution and the degradation processes that depend on the tendency of the protein to unfold (Remmele et al (2000) *Biopharm* 13:36-46,). A number of studies have found correlation between the ranking of the physical stability of formulations measured as thermal stability by DSC and physical stability measured by other methods (Gupta et al (2003) *AAPS PharmSci* 5E8; Zhang et al (2004) *J. Pharm. Sci.* 93:3076-89; Maa et al (1996) *Int. J. Pharm.* 140:155-68; Bedu-Addo et al (2004) *Pharm. Res.* 21:1353-61; Remmele et al (1997) *Pharm. Res.* 15:200-8). Formulation studies suggest that a Fab T_m has implication for long-term physical stability of a corresponding mAb. Differences in amino acids in either framework or within the CDRs could have significant effects on the thermal stability of the Fab domain (Yasui et al (1994) *FEBS Lett.* 353:143-6).

[0425] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention competes with binding to the human IFN-ω with an isolated antibody comprising the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 71.

[0426] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention competes with binding to the human IFN-ω with an isolated antibody comprising the VH of SEQ ID NO: 28 and the VL of SEQ ID NO: 150.

[0427] Competition between specific binding to human IFN-ω with antibodies of the invention comprising certain VH and VL sequences may be assayed in vitro using well known methods. For example, binding of MSD Sulfo-Tag™ NHS-ester—labeled antibody to human to human IFN-ω in the presence of an unlabeled antibody can be assessed by ELISA, or Bioacore analyses or flow cytometry may be used to demonstrate competition with the antibodies of the current invention.

[0428] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes, wherein the antibody binds IFN-ω of SEQ ID NO: 1 at least at residues F27, L30 and R33 of.

[0429] The residues F27, L30 and R33 IFN-ω define a minimal epitope required for broad neutralizing activity of the IFN-α/ω antibodies of the invention. Crystal structure of several antibody/INF-α or antibody/IFN-ω complexes revealed the three residues provide predominant contributions to antibody binding The F27 residue is conserved in all human IFN-αs except IFN-αD (al), to which antibodies of the invention do not bind. Both L30 and R33 are conserved in all human INF-αs as well as in human IFN-ω. Further confirmation of the contribution of F27 to the epitope is evident from the binding studies with various cyno IFN-α subtypes: the antibodies of the invention do not bind cyno IFN-α13, which, like human IFN-αD, has a serine at position 27 (S27).

[0430] In another embodiment described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention binds human IFN-ω of SEQ ID NO: 1 at least at residues S25, P26, F27, L28, L30, K31, R33, R34 and D35.

[0431] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes, wherein the antibody binds human IFN-ω of SEQ ID NO: 1 at one or more residues including F27.

[0432] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodiments listed below, the antibody of the invention is a bispecific antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes and binds BLyS, CD40L, IL-6,

CD27, BDCA2, IL-12, IL-23, IFN-αD, IL-17, CD20, IL-10, CD22, IL-21, ICOS, ICOSL or IFN-γ.

[0433] Given the presence of elevated IFN-ω in SLE patients, and the demonstration that IFN-ω can induce BLyS secretion in PBMCs in vitro, combined blockade of IFN-α/ω in SLE patients may be more effective at reducing BLyS levels in comparison to anti IFN-α specific approaches. The extent of IFN-signature and IFN activity in SLE patients appears to correlate with soluble BLyS levels.

[0434] The IFN-α/ω antibodies of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be engineered into bispecific antibodies which are also encompassed within the scope of the invention. The VL and/or the VH regions of the antibodies of the invention may be engineered using published methods into single chain bispecific antibodies as structures such as TandAb® designs (Int. Pat. Publ. No. WO99/57150; U.S. Pat. Publ. No. US2011/0206672) or into bispecific scFVs as structures such as those disclosed in U.S. Pat. No. US5869620; Int. Pat. Publ. No. WO95/15388, lnt. Pat. Publ. No. WO97/14719 or Int. Pat. Publ. No WO11/036460.

[0435] The VL and/or the VH regions of the antibodies of the invention may be engineered into bispecific full length antibodies, where each antibody arm binds a distinct antigen or epitope. Such bispecific antibodies are typically made by modulating the CH3 interactions between the two antibody heavy chains to form bispecific antibodies using technologies such as those described in U.S. Pat. No. 7,695,936; Int. Pat. Publ. No. WO04/111233; U.S. Pat. Publ. No. 2010/0015133; U.S. Pat. Publ. No. 2007/0287170; Int. Pat. Publ. No. WO2008/119353; U.S. Pat. Publ. No. 2009/0182127; U.S. Pat. Publ. No. 2010/0286374; U.S. Pat. Publ. No. 2011/0123532; Int. Pat. Publ. No. WO2011/131746; Int. Pat. Publ. No. WO2011/143545; or U.S. Pat. Publ. No. 2012/0149876.

[0436] For example, bispecific antibodies of the invention may be generated in vitro in a cell-free environment by introducing asymmetrical mutations in the CH3 regions of two monospecific homodimeric antibodies and forming the bispecific heterodimeric antibody from two parent monospecific homodimeric antibodies in reducing conditions to allow disulfide bond isomerization according to methods described in Intl.Pat. Publ. No. WO2011/131746. In the methods, the first monospecific bivalent antibody (e.g., anti-IFN-α/ω antibody of the invention) and the second monospecific bivalent antibody (e.g., anti-BLyS, anti-CD40L, anti- IL-6, anti-CD27, anti-BDCA2, anti- IL-12, anti-IL-23, anti-IFN-αD, anti-IL-17, anti-CD20, anti-IL-10, anti-CD22, anti-IL-21, anti-ICOS, anti- ICOSL or anti-IFN-γ antibody.) are engineered to have certain substitutions at the CH3 domain that promote heterodimer stability; the antibodies are incubated together under reducing conditions sufficient to allow the cysteines in the hinge region to undergo disulfide bond isomerization; thereby generating the bispecific antibody by Fab arm exchange. The incubation conditions may optimally be restored to non-reducing. Exemplary reducing agents that may be used are 2- mercaptoethylamine (2-MEA), dithiothreitol (DTT), dithioerythritol (DTE), glutathione, tris(2-carboxyethyl)phosphine (TCEP), L-cysteine and beta-mercaptoethanol, preferably a reducing agent selected from the group consisting of: 2-mercaptoethylamine, dithiothreitol and tris(2-carboxyethyl)phosphine. For example, incubation for at least 90 min at a temperature of at least 20° C. in the presence of at least 25 mM 2-MEA or in the presence of at least 0.5 mM dithiothreitol at a pH of from 5-8, for example at pH of 7.0 or at pH of 7.4 may be used.

[0437] Exemplary CH3 mutations that may be used in a first heavy chain and in a second heavy chain of the bispecific antibody are K409R and/or F405L. Additional bispecific structures into which the VL and/or the VH regions of the antibodies of the invention may be incorporated are for example Dual Variable Domain Immunoglobulins (DVD) (Int. Pat. Publ. No. WO2009/134776), or structures that include various dimerization domains to connect the two antibody arms with different specificity, such as leucine zipper or collagen dimerization domains (Int. Pat. Publ. No. WO2012/022811, U.S. Pat. No. 5,932,448; U.S. Pat. No. 6,833,441). DVDs are full length antibodies comprising the heavy chain having a structure VH1-linker-VH2-CH and the light chain having the structure VL1-linker-VL2-CL; linker being optional.

[0438] The VH and the VL binding BLyS, CD40L, IL-6, CD27, BDCA2, IL-12, IL-23, IFN-αD, IL-17, CD20, IL-10, CD22, IL-21, ICOS, ICOSL or IFN-γ to be incorporated into bispecific anti-IFN-α/ω antibodies may be generated de novo using methods described herein, or may be engineered from existing monospecific antibodies. Exemplary anti-BLyS antibody that may be used to generate the bispecific antibodies of the invention is BENLYSTA®. Exemplary CD40L antibodies that may be used are those described in U.S. Pat. No. 5,474,771, U.S. Pat. No. 5,747,037, Int. Pat. Publ. No. WO01/68860, Int. Pat. Publ. No.WO06/033702 or Int. Pat. Publ. No. WO08/118356. Exemplary anti-IL-6 antibodies that may be used are those described in Int. Pat. Publ. No. WO06/119115, Int. Pat. Publ. No. WO10/056948, Int. Pat. Publ. No. WO10/088444 or Int. Pat. Publ. No. WO07/076927. Exemplary anti-CD27 antibodies that may be used are those described in Int. Pat. Publ. No. WO13/138586, Int. Pat. Publ. No. WO11/130434 or Int. Pat. Publ. No. WO12/004367. Exemplary IL-12 and IL-23 antibody that may be used are STELARA® Exemplary IL-23 antibodies that may be used are those described in Int. Pat. Publ. No. WO07/005955, Int. Pat. Publ. No. WO07/027714, Int. Pat. Publ. No. WO08/103432,Int. Pat. Publ. No. WO07/106769, Int. Pat. Publ. No. WO07/147019 or Int. Pat. Publ. No. WO08/134659. Exemplary IL-17 antibodies that may be used are those described in Int. Pat. Publ. No. WO06/013107, Int. Pat. Publ. No. WO06/054059 Int. Pat. Publ. No. WO07/070750, Int. Pat. Publ. No. WO08/134659, Int. Pat. Publ. No. WO07/149032, Int. Pat. Publ. No. WO08/021156, Int. Pat. Publ. No. WO08/047134, Int. Pat. Publ. No. WO09/130459, Int. Pat. Publ. No. WO10/025400, Int. Pat. Publ. No. WO11/053763 and Int. Pat. Publ. No. WO12/095662.

[0439] Another embodiment of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, is an antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes having certain VH and VL sequences, wherein the antibody VH is encoded by a first polynucleotide and the antibody VL is encoded by a second synthetic polynucleotide. The polynucleotide may be a complementary deoxynucleic acid (cDNA), and may be codon optimized for expression in suitable host. Codon optimization is a well-known technology.

[0440] In some embodiments described herein, and in some embodiments of each and every one of the numbered embodi-

ments listed below, the polynucleotides encoding the antibody VH or VL of the invention comprise the sequences of SEQ ID NOs: 72, 92, 108, 110, 117 or 122.

[0441] Another embodiment of the invention is an isolated polynucleotide encoding any of the antibody heavy chain variable regions and/or the antibody light chain variable regions of the invention. Certain exemplary polynucleotides are disclosed herein, however, other polynucleotides which, given the degeneracy of the genetic code or codon preferences in a given expression system, encode the antibodies of the invention are also within the scope of the invention. Exemplary polynucleotides are for example polynucleotides having the sequences shown in SEQ ID NOs: 72, 92, 108, 110, 117 or 122. The polynucleotide sequences encoding a VH or a VL or a fragment thereof of the antibody of the invention may be operably linked to one or more regulatory elements, such as a promoter or enhancer, that allow expression of the nucleotide sequence in the intended host cell. The polynucleotide may be a cDNA.

[0442] Another embodiment of the invention is a vector comprising the polynucleotide of the invention. Such vectors may be plasmid vectors, viral vectors, vectors for baculovirus expression, transposon based vectors or any other vector suitable for introduction of the synthetic polynucleotide of the invention into a given organism or genetic background by any means. For example, polynucleotides encoding light and/or heavy chain variable regions of the antibodies of the invention, optionally linked to constant regions, are inserted into expression vectors. The light and/or heavy chains may be cloned in the same or different expression vectors. The DNA segments encoding immunoglobulin chains may be operably linked to control sequences in the expression vector(s) that ensure the expression of immunoglobulin polypeptides. Such control sequences include signal sequences, promoters (e.g. naturally associated or heterologous promoters), enhancer elements, and transcription termination sequences, and are chosen to be compatible with the host cell chosen to express the antibody. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the proteins encoded by the incorporated polynucleotides.

[0443] Suitable expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors contain selection markers such as ampicillin-resistance, hygromycin-resistance, tetracycline resistance, kanamycin resistance or neomycin resistance to permit detection of those cells transformed with the desired DNA sequences.

[0444] Suitable promoter and enhancer elements are known in the art. For expression in a bacterial cell, exemplary promoters include lacI, lacZ, T3, T7, gpt, lambda P and trc. For expression in a eukaryotic cell, exemplary promoters include light and/or heavy chain immunoglobulin gene promoter and enhancer elements; cytomegalovirus immediate early promoter; herpes simplex virus thymidine kinase promoter; early and late SV40 promoters; promoter present in long terminal repeats from a retrovirus; mouse metallothionein-I promoter; and various art-known tissue specific promoters. For expression in a yeast cell, an exemplary promoter is constitutive promoter such as an ADH1 promoter, a PGK1 promoter, an ENO promoter, a PYK1 promoter and the like; or a regulatable promoter such as a GAL1 promoter, a GAL10 promoter, an ADH2 promoter, a PHO5 promoter, a CUP1 promoter, a GALT promoter, a MET25 promoter, a MET3 promoter, a CYC1 promoter, a HIS3 promoter, an ADH1 promoter, a PGK promoter, a GAPDH promoter, an ADC1 promoter, a TRP 1 promoter, a URA3 promoter, a LEU2 promoter, an ENO promoter, a TP1 promoter, and AOX1 (e.g., for use in Pichia). Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art.

[0445] Large numbers of suitable vectors and promoters are known to those of skill in the art; many are commercially available for generating a subject recombinant constructs. The following vectors are provided by way of example. Bacterial: pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene, La Jolla, Calif., USA); pTrc99A, pKK223-3, pKK233-3, pDR540, and pRIT5 (Pharmacia, Uppsala, Sweden). Eukaryotic: pWLneo, pSV2cat, pOG44, PXR1, pSG (Stratagene) pSVK3, pBPV, pMSG and pSVL (Pharmacia).

[0446] Another embodiment of the invention is a host cell comprising one or more vectors of the invention. The term "host cell" refers to a cell into which a vector has been introduced. It is understood that the term host cell is intended to refer not only to the particular subject cell but to the progeny of such a cell, and also to a stable cell line generated from the particular subject cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein. Such host cells may be eukaryotic cells, prokaryotic cells, plant cells or archeal cells.

[0447] *Escherichia coli*, bacilli, such as *Bacillus subtilis*, and other enterobacteriaceae, such as *Salmonella, Serratia*, and various *Pseudomonas* species are examples of prokaryotic host cells. Other microbes, such as yeast, are also useful for expression. *Saccharomyces* (e.g., *S. cerevisiae*) and *Pichia* are examples of suitable yeast host cells Exemplary eukaryotic cells may be of mammalian, insect, avian or other animal origins. Mammalian eukaryotic cells include immortalized cell lines such as hybridomas or myeloma cell lines such as SP2/0 (American Type Culture Collection (ATCC), Manassas, Va., CRL-1581), NSO (European Collection of Cell Cultures (ECACC), Salisbury, Wiltshire, UK, ECACC No. 85110503), FO (ATCC CRL-1646) and Ag653 (ATCC CRL-1580) murine cell lines. An exemplary human myeloma cell line is U266 (ATTC CRL-TIB-196). Other useful cell lines include those derived from Chinese Hamster Ovary (CHO) cells such as CHO-K1 SV (Lonza Biologics, Walkersville, Md.), CHO-K1 (ATCC CRL-61) or DG44.

[0448] Another embodiment of the invention is a method of producing an antibody of the invention comprising culturing the host cell of the invention in conditions that the antibody is expressed, and recovering the antibody produced by the host cell. Methods of making antibodies and purifying them are well known in the art. Once synthesized (either chemically or recombinantly), the whole antibodies, their dimers, individual light and/or heavy chains, or other antibody fragments such as VH and/or VL, may be purified according to standard procedures, including ammonium sulfate precipitation, affinity columns, column chromatography, high performance liquid chromatography (HPLC) purification, gel electrophoresis, and the like (see generally Scopes, Protein Purification (Springer- Verlag, N.Y., (1982)). A subject antibody may be substantially pure, e.g., at least about 80% to 85% pure, at least about 85% to 90% pure, at least about 90% to 95% pure,

or at least about 98% to 99%, or more, pure, e.g., free from contaminants such as cell debris, macromolecules, etc. other than the subject antibody.

[0449] Another embodiment of the invention is a method for producing an antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) comprising:

[0450] incorporating the first polynucleotide encoding the VH of the antibody and the second polynucleotide encoding the VL of the antibody into an expression vector;

[0451] transforming a host cell with the expression vector;

[0452] culturing the host cell in culture medium under conditions wherein the VL and the VH are expressed and form the antibody; and

[0453] recovering the antibody from the host cell or culture medium.

[0454] The polynucleotides encoding certain VH or VL sequences of the invention are incorporated into vectors using standard molecular biology methods. Host cell transformation, culture, antibody expression and purification are done using well known methods.

Methods of Treatment

[0455] IFN-α/ω antibodies of the invention may be utilized to treat immune-mediated inflammatory diseases or autoimmune diseases such as lupus, including systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE), or other immune-mediated inflammatory diseases such as psoriasis, immune thrombocytopenia (ITP), Aicardi-Goutieres syndrome (AGS), systemic sclerosis, Sjogren's syndrome, myositis, common variable immune deficiency (CVID), autoimmune thyroid disease, type I diabetes, rheumatoid arthritis, transplant rejection or graft versus host disease (GVHD). These diseases may be associated with increased production of INF-α and/or IFN-ω or type I IFN signature.

[0456] One embodiment of the invention is a method of treating an immune-mediated inflammatory disease or an autoimmune disease, comprising administering a therapeutically effective amount of an isolated antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes to a patient in need thereof for a time sufficient to treat the immune-mediated inflammatory disease or autoimmune disease.

[0457] Another embodiment of the invention is a method of treating lupus, comprising administering a therapeutically effective amount of an isolated antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes to a patient in need thereof for a time sufficient to treat lupus.

[0458] In some embodiments, lupus is systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE).

[0459] In some embodiments, the patient has lupus nephritis.

[0460] In some embodiments, the immune-mediated inflammatory disease or the autoimmune disease is psoriasis, immune thrombocytopenia (ITP), Aicardi-Goutieres syndrome (AGS), systemic sclerosis, Sjogren's syndrome, myositis, common variable immune deficiency (CVID), autoimmune thyroid disease, type I diabetes, rheumatoid arthritis, transplant rejection or graft versus host disease (GVHD).

[0461] Another embodiment of the invention is a method of treating a chronic viral infection, comprising administering a therapeutically effective amount of an isolated antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes to a patient in need thereof for a time sufficient to treat the chronic viral infection.

[0462] IFN-I is well known to have a protective role in acute viral infection. Recently, IFN-I has been demonstrated to have an immunosuppressive role in chronic viral infections through a mechanism at least partially mediated by IL-10 and programmed cell death 1 ligand 1 (PDL1) (Teijaro et al., *Science* 340, 207-211, (2013); Wilson et al., *Science* 340, 202-207, 2013). Combined blockade of multiple INF-α subtypes and IFN-ω may offer beneficial effects in patients with chronic viral infections including HW and hepatitis C by down-modulating an immunosuppressive environment conducive to viral persistence.

[0463] In some embodiments, the chronic viral infection is HIV or hepatitis C.

[0464] "Treatment" or "treat" refers to therapeutic treatment. Patients that may be treated also include those prone to or susceptible to have the disorder, of those in which the disorder is to be prevented. Individuals in need of treatment include those already with the disorder or a symptom of the disorder. Beneficial or desired clinical results include alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0465] Exemplary antibodies that may be used in the methods of the invention comprise VH, VL, HCDR and/or LCDR regions as shown in tables 9, 13, 15, 17, 19, 21, 22, 23, 24, 25, 26 or 27, and antibodies IFWM3308, IFWM3307, IFWM3410, IFWM3322, IFWM3385, IFWM3416, IFWM3310, IFWM3400, IFWM3321, IFWM3522, IFWM3524, IFWM3320, IFWM3304, IFWM3520, IFWM3399, IFWM3314, IFWM3331, IFWM3405, IFWM3442, IFWM3525, IFWM3423, IFWM3444 and IFWM3421.

[0466] Other exemplary antibodies that may be used in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below are antibodies that bind to and neutralize a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes, wherein the antibody binds IFN-ω of SEQ ID NO: 1 at least at residues F27, L30 and R33.

[0467] Other exemplary antibodies that may be used in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, are antibodies that bind human IFN-ω of SEQ ID NO: 1 at least at residues S25, P26, F27, L28, L30, K31, R33, R34 and D35.

[0468] The methods of the invention may be used to treat an animal patient belonging to any classification. Examples of such animals include mammals such as humans, rodents, dogs, cats and farm animals.

[0469] The antibodies of the invention may be useful in the preparation of a medicament for such treatment, wherein the medicament is prepared for administration in dosages defined herein. SLE is a chronic multiorgan autoimmune disease with both genetic and environmental factor contributing to its development.

[0470] SLE is characterized by production of pathogenic autoantibodies and tissue deposition of immune complexes, resulting in tissue damage across multiple organs. Combinations of cutaneous, musculoskeletal, hematological, neurological and renal complications are seen in patients, with periods of flare-ups and remissions. Lupus nephritis is defined as a case of SLE with a diagnosis of nephritis, proteinuria, hematuria and/or renal failure. In lupus nephritis patients, renal involvement is characterized by proteinuria (>0.5 g/24 hours), and/or red blood cells or casts in urine specimens.

[0471] Not wishing to be bound by any particular theory, it is suggested that SLE triggers, such autoantibody immune complexes, invoke type I IFN responses associated with overproduction of IFN-α and IFN-ω, but not IFN-β. Therefore, IFN-α/ω antibodies of the invention may provide a more efficacious treatment of lupus and other immune-mediated inflammatory disease, broadly inhibiting IFN-ω and multiple INF-α subtypes while sparing IFN-β function, which may play a more critical role in antiviral defense and which molecule may have no biological releavance in lupus. For example, anti-IFN-β antibodies failed to neutralize patient serum activity from both SLE and AGS patients, a disease also associated with elevated type IFN-I activity and IFN signature (Hooks et al., Arthritis and Rheumatism 25:396-400, 1982; Hua et al., Arthritis and Rheumatism 54: 1906 (June 2006); Rice et al., Lancet Neurology doi:10.1016/S1474-4422(13)70258-8 (2013)).

[0472] Other types of lupus in addition to SLE include cutaneous lupus erythematosus (CLE) and pediatric lupus.

[0473] Symptoms associated with lupus include joint pain and stiffness, nonerosive arthritis, muscle aches, pains, weakness, fever, malaise, ulcers on oral tissues, cutaneous manifestations (e.g., butterfly-shaped rash across the nose and cheeks; sunlight-induced dermatological flares), unusual weight loss or weight gain, anemia, low lymphocyte and/or platelet counts, neurological or neuropsychiatric manifestations (e.g., trouble thinking, memory problems, confusion, depression, headache, seizures, strokes), kidney problems (e.g., nephritis, e.g., glomerulonephritis), sun or light sensitivity, hair loss, purple or pale fingers from stress or cold, vascular lesions or other vascular manifestations, or cardiopulmonary symptoms such as pericarditis or pleuritis. Elevated levels of interleukins IL-1, IL-6, IL-10, 11-12, IL-17, IL-18, IL-5 and IL-16; TNF-α or Type I interferons, as well as overexpression of IFN inducible genes is documented in lupus patients. Patients may have elevated levels of autoantibodies against nuclear and cellular components such as double stranded DNA (dsDNA), ribonucleoprotein (RNP), SS-a/Ro, SS-b/La, phospholipids, histones or cardiolipin. Patients may have immune complex deposition in at least one tissue.

[0474] SLE may be diagnosed or classified for example using recommendations by the American College of Rheumatology (ACR), or by the Systemic Lupus International Collaborating Clinics Criteria (SLICC) for the Classification of Systemic Lupus Erythematosus. For example, the 2012 SLICC criteria require that patients demonstrate at least 4 of 11 criteria, with at least one clinical and one immunologic criterion, or lupus nephritis verified with biopsy in the presence of anti-DNA antibodies (ADA) or anti-nucleic acid antibodies (ANA). Clinical criteria are acute cutaneous lupus, chronic cutaneous lupus, oral or nasal ulcers, non-scarring alopecia, arthritis, serositis, renal symptoms, neurologic symptoms, hemolytic anemia, leukopenia or thrombocytopenia (<100,000/mm^3) Immunologic criteria include ANA, ADA, anti-Sm, anti-phospholipid antibodies, low complement (C3, C4 or CHSO) or direct Coombs' test, which does not count in the presence of hemolytic anemia (Petre et al., Arthritis and Rheumatism Aug 2012). Active disease may be defined by one British Isles Lupus Activity Group's (BILAG) "A" criteria or two BILAG "B" criteria; SLE Disease Activity Index (SLEDAI); or systemic lupus erythematosus (SLE) responder index (SRI) described in Furie et al., Arthritis Rheum. 61(9): 1143-51 (2009).

[0475] SLE severity and disease activity may be defined by a BILAG score by a clinician with expertise in SLE. The BILAG 2004 index is used to determine the BILAG score (see Yee, et al. Arthritis & Rheumatism 54:3300-3305, 2006; Isenberg et al., Rheumatology 44:902-906; 2005). The BILAG 2004 index assesses 97 clinical signs, symptoms, and laboratory parameters across nine organ system domains: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal, and hematological. The 97 symptoms are rated with respect to severity over the previous month (4 weeks) and with respect to any change from the previous examination (new, improving, stable, worsening, absent). A single alphabetic score (A through E) for each of the nine domains is then derived from the examination results in each organ category. Table 2 shows the BILAG categories.

TABLE 2

Category	Definition
A	Severe disease activity requiring any of the following treatment: 1. Systemic high dose oral glucocorticoids (equivalent to prednisolone >20 mg/day); 2. Intravenous pulse glucocorticoids (equivalent to pulse methylprednisolone ≥500 mg); 3. Systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis); 4. Therapeutic high dose anticoagulation in the presence of high dose steroids or immunomodulators, e.g., warfarin with target INR 3-4.
B	Moderate disease activity requiring any of the following treatment: 1. Systemic low dose oral glucocorticoids (equivalent to prednisolone ≤20 mg/day); 2. Intramuscular or intra-articular or soft tissue glucocorticoids injection (equivalent to methylprednisolone <500 mg).
C	Stable mild disease.
D	Inactive disease but previously affected.
E	System never involved.

[0476] CLE is further classified to acute (ACLE), subacute (SCLE), chronic (CCLE) or intermittent (ICLE) CLE depending on the constellation of clinical features and duration of the cutaneous lesions, laboratory abnormalities, and skin biopsy histological changes. Classification and clinical

manifestations of the various CLE forms are reviewed in Kuhn and Landmann, J Autiommunity 48-49:14-19, 2014.

[0477] A type I IFN gene signature has been reported to positively correlate with both clinical and serological features of lupus (Karageorgas et al. , J Biomed Biotechnol 273907, 2011 Baechler et al., Proc Natl Acad Sci USA 100:2610-2615, 2003, Bennett et al., J Exp Med 197:711-723, 2003, Dall'era et al. Ann Rheum Dis 64: 1692-1697, 2005, Niewold et al. Genes Immun 8: 492-502,2007).). A preponderance of autoantibodies in conjunction with their impaired clearance leads to a feedback cycle of IFN production where Fc receptor-dependent internalization of immune complexes into plasmacytoid dendritic cells (pDC) leads to increased amounts of IFN and thus establishment of the IFN signature. In clinical trials, anti-INF-α antibodies in SLE patients have demonstrated partial reduction of the type I IFN signature in the majority of patients exhibiting the IFN signature and slight efficacy in exploratory analysis (Petri et al., *Arthritis and rheumatism* 65, 1011 (Apr, 2013); Merrill Jet al., *Annals of the rheumatic diseases* 70, 314 (2011); Kennedy et al., *The 10th International Congress on SLE, Buenos Aires, Argentina* Oral Presentation 5, 022, (Apr. 20, 2013)).

[0478] The standard of care in lupus management is based on current, accepted medical practice patterns, approved guidance documents developed by rheumatology societies (e.g. American College of Rheumatology, European League Against Rheumatism) and the discretion of treating physicians. Lupus patients continue to have disease activity long after the diagnosis is made, even with proper management, often involving new organ systems or specific organ system damage. There are three patterns of disease activity in lupus: the flare (or remitting, relapsing disease activity), chronically active disease, and long quiescence. These disease patterns are characterized using systematic clinical assessments, routine laboratory tests, standardized measures of disease activity, and integration of these assessments with the patient's own perceptions of health status and quality of life. As the patient's signs and symptoms of flare persist or worsen, the physician may find that a change in medications and/or dosages is warranted. The medications used to control lupus include, but is not limited to the following: (1) NSAIDs, including over-the-counter NSAIDs, e.g., naproxen (Aleve) and ibuprofen (Advil, Motrin, others), and stronger NSAIDs available by prescription; (2) Antimalarial drugs, e.g., hydroxychloroquine (Plaquenil); (3) Corticosteroids., e.g., Prednisone and other types of corticosteroids, and (4) Immune suppressants, e.g., cyclophosphamide (Cytoxan), azathioprine (Imuran, Azasan), mycophenolate (Cellcept), leflunomide (Arava) and methotrexate (Trexall).

[0479] The antibodies of the invention may be tested for their efficacy in vitro in disease relevant cells using disease relevant IFN preparations. Such in vitro testing may be for example evaluation of inhibition of IFN production induced by SLE patient immune complexes in whole blood, or assessment of ability of the antibodies to reduce the IFN signature in whole blood as described herein Animal models of lupus may also be used, such as NZB/NZW F1 mice that exhibit a time-dependent and female-biased disease with several features of human lupus including glomerulonephritis. However, as mice do not produce IFN-ω their utilization as a model to assess efficacy of the antibodies of the invention is more limited.

[0480] In some embodiments, the patient exhibits a Type I interferon signature. "Type I interferon signature" or "interferon signature" as used herein refers to the upregulation of a subset of genes that are induced by IFN-I. Various type I IFN signatures are known, ranging from 3-27 genes. These signatures may be utilized for example as pharmacodynamics markers to assess target engagement of Type I IFN inhibitors for treatment of SLE and for purpose of SLE patient stratification.

[0481] An exemplary Type I interferon signature is shown in Table 3, consisting of 21 upreguated genes as described in Yao et al., *Arthritis and rheumatism* 60, 1785 (June 2009). Other exemplary type I interferon signatures are described in Tcherepanova, I., et al., *Annals of the rheumatic diseases* 71(Supp13) (2012) and Richardson, B. et al. Development of A Quantitative PCR Method to Determine Interferon Signature Metric Status in SLE Patients: Distribution and Clinical & Serological Associations in Two Lupus Clinical Trials. *ACR/ARHP* 2012 *Annual Meeting* Abstract 620 (2012).

[0482] In some methods, the anti-IFN-α/ω antibody is a bispecific antibody. In some methods, the anti-IFN-α/ω bispecific antibody neutralizes BLyS, CD40L, IL-6, CD27, BDCA2, IL-12, IL-23, IFN-αD, IL-17 or CD20.

TABLE 3

Number	Gene Symbol	Gene Name
1	IFI27	interferon, alpha-inducible protein 27
2	IFI6	interferon, alpha-inducible protein 6
3	RSAD2	radical S-adenosyl methionine domain containing 2
4	IFI44	Interferon-induced protein 44
5	IFI44L	IFI44L interferon-induced protein 44-like
6	USP18	ubiquitin specific peptidase 18
7	LY6E	lymphocyte antigen 6 complex, locus E
8	OAS1	2',5'-oligoadenylate synthetase 1, 40/46 kDa
9	SIGLEC1	SIGLEC1 sialic acid binding Ig-like lectin 1
10	ISG15	ISG15 ubiquitin-like modifier
11	IFIT1	interferon-induced protein with tetratricopeptide repeats
12	OAS3	OAS3 2'-5'-oligoadenylate synthetase 3, 100 kDa
13	HERC5	hect domain and RLD 5
14	MX1	myxovirus (influenza virus) resistance 1
15	LAMP3	lysosomal-associated membrane protein 3
16	EPSTI1	epithelial stromal interaction 1 (breast)
17	IFIT3	interferon-induced protein with tetratricopeptide repeats
18	OAS2	2'-5'-oligoadenylate synthetase 2, 69/71 kDa
19	RTP4	receptor (chemosensory) transporter protein 4
20	PLSCR1	Phospholipid scramblase 1
21	DNAPTP6	DNA polymerase-transactivated protein 6

Administration/Pharmaceutical Compositions

[0483] The invention provides for pharmaceutical compositions comprising the anti-IFN-α/ω antibody of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, and a pharmaceutically acceptable carrier. For therapeutic use, anti-IFN-α/ω antibody of the invention may be prepared as pharmaceutical compositions containing an effective amount of anti-IFN-α/ω antibody as an active ingredient in a pharmaceutically acceptable carrier. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the active compound is administered. Such vehicles may be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. For example, 0.4% saline

and 0.3% glycine can be used. These solutions are sterile and generally free of particulate matter. They may be sterilized by conventional, well-known sterilization techniques (e.g., filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, stabilizing, thickening, lubricating and coloring agents, etc. The concentration of the molecules or antibodies of the invention in such pharmaceutical formulation may vary widely, i.e., from less than about 0.5%, usually to at least about 1% to as much as 15 or 20%, 25%, 30%, 35%, 40%, 45% or 50% by weight and will be selected primarily based on required dose, fluid volumes, viscosities, etc., according to the particular mode of administration selected. Suitable vehicles and formulations, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in e.g. Remington: The Science and Practice of Pharmacy, 21s^t Edition, Troy, D. B. ed., Lipincott Williams and Wilkins, Philadelphia, Pa. 2006, Part 5, Pharmaceutical Manufacturing pp 691-1092, See especially pp. 958-989.

[0484] The mode of administration of the anti-IFN-α/ω antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be any suitable route such as parenteral administration, e.g., intradermal, intramuscular, intraperitoneal, intravenous or subcutaneous, pulmonary, transmucosal (oral, intranasal, intravaginal, rectal) or other means appreciated by the skilled artisan, as well known in the art.

[0485] The anti-IFN-α/ω antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be administered to a patient by any suitable route, for example parentally by intravenous (i.v.) infusion or bolus injection, intramuscularly or subcutaneously or intraperitoneally. i.v. infusion may be given over for, example, 15, 30, 60, 90, 120, 180, or 240 minutes, or from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 hours.

[0486] The dose given to a patient having an immune-mediated inflammatory disease or an autoimmune disease such as lupus is sufficient to alleviate or at least partially arrest the disease being treated ("therapeutically effective amount") and may be sometimes 0.005 mg/kg to about 100 mg/kg, e.g. about 0.05 mg/kg to about 20 mg/kg or about 0.1 mg/kg to about 20 mg/kg, or about 1 mg to about 20 mg/kg, or about 4 mg/kg, about 8 mg/kg, about 16 mg/kg or about 24 mg/kg , or, e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mg/kg, but may even higher, for example about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 40, 50, 60, 70, 80, 90 or 100 mg/kg.

[0487] A fixed unit dose may also be given, for example, 50, 100, 200, 500 or 1000 mg, or the dose may be based on the patient's surface area, e.g., 500, 400, 300, 250, 200, or 100 mg/m^2. Usually between 1 and 8 doses, (e.g., 1, 2, 3, 4, 5, 6, 7 or 8) may be administered to treat the immune-mediated inflammatory disease, such as lupus, but 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more doses may be given.

[0488] The administration of the anti-IFN-α/ω antibody in the methods of the invention and in some embodiments of each and every one of the numbered embodiments listed below, may be repeated after one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, two months, three months, four months, five months, six months or longer. Repeated courses of treatment are also possible, as is chronic administration. The repeated administration may be at the same dose or at a different dose. For example, the anti-IFN-α/ω antibody in the methods of the invention may be administered at 0.1 mg/kg, at 1 mg/kg, at 5 mg/kg, at 8 mg/kg or at 16 mg/kg at weekly interval for 8 weeks, followed by administration at 8 mg/kg or at 16 mg/kg every two weeks for an additional 16 weeks, followed by administration at 8 mg/kg or at 16 mg/kg every four weeks by intravenous infusion.

[0489] The anti-IFN-α/ω antibody may be administered in the methods of the invention and in some embodiments of each and every one of the numbered embodiments listed below, by maintenance therapy, such as, e.g ., once a week for a period of 6 months or more.

[0490] For example, the anti-IFN-α/ω antibody in the methods of the invention and in some embodiments of each and every one of the numbered embodiments listed below, may be provided as a daily dosage in an amount of about 0.1-100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 after initiation of treatment, or any combination thereof, using single or divided doses of every 24, 12, 8, 6, 4, or 2 hours, or any combination thereof.

[0491] The anti-IFN-α/ω antibody in the methods of the invention and in some embodiments of each and every one of the numbered embodiments listed below, may also be administered prophylactically in order to reduce the risk of developing the immune-mediated inflammatory disease or an autoimmune disease such as lupus, delay the onset of the immune-mediated inflammatory disease of the autoimmune disease, and/or reduce the risk of recurrence when the immune-mediated inflammatory disease or the autoimmune disease such as lupus is in remission.

[0492] Thus, a pharmaceutical composition of the invention for intramuscular injection may be prepared to contain 1 ml sterile buffered water, and between about 1 ng to about 100 mg/kg, e.g. about 50 ng to about 30 mg/kg or more preferably, about 5 mg to about 25 mg/kg, of the anti-IFN-α/ω antibody of the invention.

[0493] For example, a pharmaceutical composition comprising the anti-IFN-α/ω antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, for intravenous infusion may be made up to contain about 200 ml of sterile Ringer's solution, and about 8 mg to about 2400 mg, about 400 mg to about 1600 mg, or about 400 mg to about 800 mg of the anti-INF-α/ω antibody for administration to a 80 kg patient. Methods for preparing parenterally administrable compositions are well known and are described in more detail in, for example, "Remington's Pharmaceutical Science", 15th ed., Mack Publishing Company, Easton, Pa.

[0494] The "therapeutically effective amount" of the IFN-α/ω antibodies of the invention effective in the treatment of an immune-mediated inflammatory disease or an autoimmune disease may be determined by standard research techniques. For example, in vitro assays may be employed to help identify optimal dosage ranges. Optionally, the dosage of the IFN-α/ω antibodies of the invention that may be effective in the treatment of immune-mediated inflammatory diseases or autoim-

mune diseases such as lupus including SLE may be determined by administering the IFN-α/ω antibodies to relevant animal models well known in the art. Selection of a particular effective dose can be determined (e.g., via clinical trials) by those skilled in the art based upon the consideration of several factors. Such factors include the disease to be treated or prevented, the symptoms involved, the patient's body mass, the patient's immune status and other factors known by the skilled artisan. The precise dose to be employed in the formulation will also depend on the route of administration, and the severity of disease, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems. The antibodies of the invention may be tested for their efficacy and effective dosage using any of the models described herein.

[0495] The anti-IFN-α/ω antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional protein preparations and well known lyophilization and reconstitution techniques can be employed.

[0496] The anti-IFN-α/ω antibody in the methods of the invention described herein, and in some embodiments of each and every one of the numbered embodiments listed below, may be administered in combination with a second therapeutic agent simultaneously, sequentially or separately.

[0497] The second therapeutic agent may be a corticosteroid, an antimalarial drug, an immunosuppressant, a cytotoxic drug, or a B-cell modulator.

[0498] In some embodiments, the second therapeutic agent is prednisone, prednisolone, methylprednisolone, deflazcort, hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil (MMF), mycophenolate sodium, cyclosporine, leflunomide, tacrolimus, rituximab™, or belimumab™.

Further Embodiments of the Invention

[0499] Set out below are certain further embodiments of the invention according to the disclosures elsewhere herein. Features from embodiments of the invention set out above described as relating to the invention disclosed herein also relate to each and every one of these further numbered embodiments.

[0500] 1) An isolated monoclonal antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes.

[0501] 2) The antibody according to embodiment 1, wherein the biological activity of the human IFN-ω and the human INF-α subtypes is the human IFN-ω or the human IFN-α subtype-induced expression of secreted embryonic alkaline phosphatase (SEAP) under interferon inducible ISG54 promoter in HEK293 cells stably expressing signal transducer and activator of transcription 2 (STAT2), interferon regulatory factor 9 (IRF9) and SEAP.

[0502] 3) The antibody according to embodiment 1 or 2, wherein the antibody neutralizes the biological activity of the human IFN-ω with an IC_{50} of at least about 1×10^{-9}M or less, about 1×10^{-10} M or less, about 5×10^{-11}M or less, or about 1×10^{-11}M or less.

[0503] 4) The antibody according to any one of embodiments 1-3, wherein the antibody neutralizes the biological activity of the human IFN-ω with an IC_{50} value of at least about 1×10^{-10} M or less.

[0504] 5) The antibody according to any one of embodiments 1-4, wherein the antibody neutralizes the activity of the human IFN-ω with an IC_{50} value of between about 1×10^{-10}M to about 6×10^{-12}M.

[0505] 6) The antibody according to any one of embodiments 1-5, wherein the antibody neutralizes the activity of at least three, four, five, six, seven, eight, nine, ten or eleven human INF-α subtypes with an IC_{50} value of at least about 1×10^{-10} M or less.

[0506] 7) The antibody according to embodiment 6, wherein the INF-α subtypes are selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJl, IFN-αK, IFN-αWA and IFN-α4a.

[0507] 8) The antibody according to embodiment 7, wherein the antibody comprises heavy chain complementarity determining region (HCDR) 1 (HCDR1), 2 (HCDR2) and 3 (HCDR3) amino acid sequences of SEQ ID NOs: 109, 114 and 121, respectfully, and light chain complementarity determining region (LCDR) 1 (LCDR1), 2 (LCDR2) and 3 (LCDR3) amino acid sequences of SEQ ID NOs: 118, 119 and 120.

[0508] 9) The antibody according to any one of embodiments 1-5, wherein the antibody neutralizes at least six human INF-α subtypes selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJl, IFN-αK, IFN-αWA and IFN-α4a.

[0509] 10) The antibody according to embodiment 9, wherein the antibody comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 114, 121, 159, 119 and 160, respectively.

[0510] 11) The antibody according to any one of embodiments 1-5, wherein the antibody neutralizes at least ten human INF-α subtypes selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αK, IFN-αWA and IFN-α4a.

[0511] 12) The antibody according to embodiment 11, wherein the antibody binds human IFN-ω of SEQ ID NO: 1 at least at amino acid residues F27, L30 and R33.

[0512] 13) The antibody according to any one of embodiments 1-5, wherein the antibody comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 114, 121, 161, 119 and 162, respectively.

[0513] 14) The antibody according to any one of embodiments 11-13, wherein the antibody neutralizes at least the human INF-α subtypes IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αJl and IFN-α4a.

[0514] 15) The antibody according to embodiment 14, wherein the antibody further neutralizes IFN-αI, IFN-αK or IFN-αWA.

[0515] 16) The antibody according to any one of embodiments 1-15, wherein the antibody

[0516] a) inhibits leukocyte interferon-induced IP-10 release in whole blood induced by 250U/ml of interferon by about 50% or more in the presence of 10 μg/ml antibody; or

[0517] b) inhibits systemic lupus erythematosus (SLE) immune complex-induced IP-10 release in whole blood by about 50% or more in the presence of 10 μ/ml antibody.

[0518] 17) The antibody according to any one of embodiments 1-16, wherein the antibody comprises a heavy chain variable region (VH) amino acid sequence at least 90%, 91%, 92%, 93%, 94%, 95% , 96%, 97%, 98% or 99% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 90%, 91%, 92%, 93%, 94%, 95% , 96%, 97%, 98% or 99% identical to SEQ ID NO: 150.

[0519] 18) The antibody according to any one of embodiments 1-17, comprising

[0520] a) the HCDR1 amino acid sequences of SEQ ID NOs: 109;

[0521] b) the HCDR2 amino acid sequences of SEQ ID NOs: 111, 112 or 113;

[0522] c) the HCDR3 amino acid sequences of SEQ ID NOs: 115 or116 ;

[0523] d) the LCDR1 amino acid sequences of SEQ ID NOs: 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91;

[0524] e) the LCDR2 amino acid sequences of SEQ ID NOs: 93, 94 or 95; and

[0525] f) the LCDR3 amino acid sequences of SEQ ID NOs: 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106 or 107.

[0526] 19) The antibody according to embodiment 18, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 sequences of SEQ ID NOs:

[0527] a) 109, 113, 116, 77, 93 and 104, respectively;

[0528] b) 109, 113, 116, 85, 93 and 96, respectively;

[0529] c) 109, 113, 115, 79, 95 and 107, respectively;

[0530] d) 109, 113, 116, 76, 93 and 103, respectively;

[0531] e) 109, 113, 115, 85, 93 and 96, respectively;

[0532] f) 109, 113, 115, 89, 95 and 100, respectively;

[0533] g) 109, 113, 116, 86, 93 and 105, respectively;

[0534] h) 109, 113, 115, 76, 93 and 103, respectively;

[0535] i) 109, 113, 116, 80, 93 and 97, respectively;

[0536] j) 109, 113, 116, 84, 93 and 97, respectively;

[0537] k) 109, 113, 116, 90, 93 and 97, respectively;

[0538] l) 109, 113, 116, 88, 93 and 102, respectively;

[0539] m) 109, 113, 116, 87, 93 and 105, respectively;

[0540] n) 109, 113, 116, 91, 93 and 106, respectively;

[0541] o) 109, 113, 115, 80, 93 and 97, respectively;

[0542] p) 109, 113, 116, 83, 93 and 101, respectively;

[0543] q) 109, 113, 116, 82, 94 and 98, respectively;

[0544] r) 109, 113, 115, 78, 95 and 100, respectively;

[0545] s) 109, 111, 116, 81, 93 and 106, respectively;

[0546] t) 109, 113, 116, 82, 94 and 99, respectively;

[0547] u) 109, 113, 115, 81, 93 and 106, respectively;

[0548] v) 109, 112, 116, 81, 93 and 106, respectively; or

[0549] w) 109, 113, 116, 81, 93 and 106, respectively.

[0550] 20) The antibody according to any one of embodiments 1-19, wherein the antibody is humanized or human. 21) The antibody according to embodiment 20, wherein the human antibody heavy chain variable region framework is derived from human germline gene IGHV5-51 (SEQ ID NO: 155).

[0551] 22) The antibody according to embodiment 21, wherein the human antibody light chain variable region framework is derived from human germline gene IGKV1D-39 (SEQ ID NO: 156).

[0552] 23) The antibody according to any one of embodiments 1-22, wherein the antibody is of IgG1, IgG2, IgG3 or IgG4 subtype.

[0553] 24) The antibody according to embodiment 23, wherein the antibody has at least one substitution in an Fc region.

[0554] 25) The antibody according to embodiment 24, wherein the wherein the substitution comprises a substitution M252Y/S254T/T256E, V234A/G237A/P238S/H28AN309L/A330S/P331S or P238S/L234A/L235A, wherein residue numbering is according to the EU numbering.

[0555] 26) The antibody according to any one of embodiments 1-26, comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the

[0556] a) VH comprises the amino acid sequence of SEQ ID NOs: 28, 31, 157 or 158.

[0557] 27) The antibody according to embodiment 26, wherein the VL comprises the amino acid sequence of SEQ ID NOs: 35, 39, 40, 42, 46, 52, 53, 54, 57, 61, 62, 68, 71, 73, 75, 135 or 150.

[0558] 28) The antibody according to embodiment 27 comprising the VH and the VL of SEQ ID NOs:

[0559] a) 28 and 40, respectively;

[0560] b) 28 and 39, respectively;

[0561] c) 31 and 62, respectively;

[0562] d) 28 and 54, respectively;

[0563] e) 31 and 39, respectively;

[0564] f) 31 and 68, respectively;

[0565] g) 28 and 42, respectively;

[0566] h) 31 and 54, respectively;

[0567] i) 28 and 53, respectively;

[0568] j) 28 and 73, respectively;

[0569] k) 28 and 75, respectively;

[0570] l) 28 and 52, respectively;

[0571] m) 28 and 35, respectively;

[0572] n) 28 and 135, respectively;

[0573] o) 31 and 53, respectively;

[0574] p) 28 and 46, respectively;

[0575] q) 28 and 61, respectively;

[0576] r) 31 and 57, respectively;

[0577] s) 157 and 71, respectively;

[0578] t) 28 and 150, respectively;

[0579] u) 31 and 71, respectively;

[0580] v) 158 and 71, respectively; or

[0581] w) 28 and 71, respectively.

[0582] 29) The antibody according to any one of embodiments 1-28, wherein the antibody is bispecific.

[0583] 30) The antibody according to embodiment 29, wherein the antibody binds BLyS, CD40L, IL-6, CD27, BDCA2, IL-12, IL-23, IFN-αD, IL-17, CD20, IL-10, CD22, IL-21, ICOS, ICOSL or IFN-γ.

[0584] 31) A pharmaceutical composition comprising the antibody according to any one of embodiments 1-30 and a pharmaceutically accepted carrier.

[0585] 32) A polynucleotide encoding the antibody VH or VL or the antibody VH and VL of any one of embodiments 1-28.

[0586] 33) A vector comprising the polynucleotide of embodiment 32.

[0587] 34) A host cell comprising the vector of embodiment 33.

[0588] 35) A method of producing the antibody of embodiment 19, comprising culturing the host cell of embodiment 33 in conditions that the antibody is expressed, and recovering the antibody produced by the host cell.

[0589] 36) The antibody according to any one of embodiments 1-30 for use in the treatment of an immune-mediated inflammatory disease or an autoimmune disease.

[0590] 37) The antibody according to embodiment 36 for use of

[0591] a) the immune-mediated inflammatory disease or the autoimmune disease, wherein the immune-mediated inflammatory disease or the autoimmune disease is optinally lupus, psoriasis, immune thrombocytopenia (ITP), Aicardi-Goutieres syndrome (AGS), systemic sclerosis, Sjogren's syndrome, myositis, common variable immune deficiency (CVID), autoimmune thyroid disease, type I diabetes, rheumatoid arthritis, transplant rejection or graft versus host disease (GVHD);

[0592] b) chronic viral infection, wherein the chronic viral infection is optionally HIV or hepatitis C infection.

[0593] 38) The antibody according to any one of embodiments 1-30 for use in the treatment of lupus.

[0594] 39) The antibody according to embodiment 38 for use of lupus, wherein lupus is systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE).

[0595] 40) The antibody according to any one of embodiments 1-30 for use in the treatment of an immune-mediated inflammatory disease or lupus, wherein the patient to be treated has

[0596] a) lupus nephritis; or

[0597] b) exhibits a Type I interferon signature.

[0598] 41) The antibody according to any one of embodiments 1-30 for use according to embodiments 37-40 in combination with a second therapeutic agent.

[0599] 42) The antibody according to embodiment 41, wherein the second therapeutic agent is a) an antibody that binds BLyS, CD40L, IL-6, CD27, BDCA2, IL-12, IL-23, IFN-αD, IL-17, CD20, IL-10, CD22, IL-21, ICOS, ICOSL or IFN-γ;

[0600] b) a corticosteroid, an antimalarial drug, an immunosuppressant, a cytotoxic drug, or a B-cell modulator; or

[0601] c) prednisone, prednisolone, methylprednisolone, deflazcort, hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil (MMF), mycophenolate sodium, cyclosporine, leflunomide, tacrolimus, rituximab™ or belimumab™.

[0602] 43) The antibody according to any one of embodiments 1-30, wherein the antibody does not neutralize IFN-αD, IFN-α1 and/or IFN-β.

[0603] The present invention will now be described with reference to the following specific, non-limiting examples.

Materials and Methods

ISRE Reporter Gene Assay ("ISRE Reporter Gene Assay")

[0604] HEK-Blue™ IFN-α/β cells (InvivoGen, San Diego, Calif.) engineered to express a fully active type I IFN signaling pathway (stably expressing STAT2 and IRF9) and transfected with a SEAP reporter gene under the control of the IFN-α/β inducible ISG54 promoter was used. The cells were grown in collagen type I coated T150 flasks in Dulbecco's modified eagle media with 10% fetal bovine serum, 100 ug/mlblasticidin and 30 ug/ml zeocin at 37° C., 5% CO_2. Cells were harvested and plated in 384-well plates at 50 μl per well at 50,000 cells per ml. Plated cells were incubated at 37° C., 5% CO_2 for 24 hr. Tested interferon samples were prepared and diluted in spent HEK ISRE serum free medium, and 50 μl of IFN sample was added to each well. Plated cells were incubated at 37° C., 5% CO_2 for 20 hr. Alkaline phosphatase was detected from 20 μl of plated cell supernatants with 60 μl/well QUANTI-Blue™ resuspended in filtered water after incubation for 20 min at room temperature. Optical density was read on a Biotek Synergy plate reader at 650 nm.

[0605] Some ISRE reporter gene assays were done in 96-well plates as follows: HEK-Blue™ IFN-α/β cells (InvivoGen, San Diego, Calif.) were plated at 50,000 cells per well in 100 μl of selection free media (DMEM+Glutamax/10% FBS, Gibco) and allowed to incubate overnight at 37° C. The next day, type I IFN stimuli were prepared (i.e. recombinant interferon, leukocyte IFN, IC induced IFN preps, serum, etc) with or without type I IFN inhibitors in a separate 96 well U-bottom transfer plate (BD Falcon) and prewarmed at 37° C. for 10 minutes. A plate of cells was removed from incubator and media was removed and replaced with 100 μl of appropriate treatments prepared in 96 well U-bottom transfer plate. Cells were placed back at 37° C. for 24 hours. The next day, 40 μl of supernatant was transferred to a 96 well flat bottom plate (BD Falcon) containing160 μl of QUANTI-Blue™ SEAP substrate (Invivogen). Plate was allowed to develop for about 15 minutes at which time it was read using a spectrometer at an absorbancy of 650 nm.

EXAMPLE 1

Soluble IFN-ω is Present and Active in the Blood of SLE Patients

[0606] Plasma from two independent SLE cohorts from Nanjing China and serum collected from a Caucasian cohort in the USA were analyzed for soluble IFN-ω and IFN-α using a multiplex ELISA using a VeriPlex human interferon multiplex ELISA kit (PBL Assay Science, cat no 51500-1) according to manufacturer's instructions. The multiplex ELISA detects many, but not all of the IFN-α subtypes and may not accurately reflect quantitative differences between total IFN-α levels versus IFN-ω.

[0607] IFN-ω, in addition of IFN-α, was found to be elevated in certain patients from both Nanjing China cohort (FIG. **1**A) and Caucasian cohort (FIG. **1**B) from each cohort. FIG. **1**A shows results from only those patients that were found to have elevated INF-α or IFN-ω. Serum samples from the Caucasian group were further screened for IFN-I activity using an ISRE reporter gene assay. Donors exhibiting the greatest amount of detectable IFN protein by ELISA also

demonstrated the greatest level of ISRE induction in the reporter gene assay (FIG. **1**C).

EXAMPLE 2

Combined Blockade of IFN-ω and INF-α Results in Greater Inhibition of SLE Immune Complex-Induced IFN than INF-α Blockade Alone

[0608] Effect of inhibition of IFN-α alone or both IFN-ω and IFN-α to reduce SLE immune complex-induced IFN, a stimulus better representing the type I IFN milieu present in SLE, was evaluated. SLE immune complex-induced IFN was prepared by stimulating human PBMCs with immune complexes prepared from two individual SLE donors and this conditioned media was utilized in a type I IFN-inducible reporter gene assay (ISRE reporter gene assay) in the presence of IFN inhibitors and controls.

Immune Complex Preparation

[0609] SLE donor 232 and 293 plasma (prescreened for IFN activity) and healthy control plasma (Astarte Biologics) was utilized for IgG purification using protein A/G columns (Thermo Scientific, Cat# 89958) according to the manufacturer's instructions. Serum from a pooled healthy donor preparation (Life Technologies, Cat# 34005100) was used for purification of healthy control IgG. To create lysates for immune complex formation, HEK293T cells (ATCC, Cat# CRL-3216) were concentrated to 5×10^7 cells/ml in 1× DPBS (Life Technologies, Cat#14190-250). To create lysates, freeze—thawing was performed for 4 cycles of 10 minutes, freezing at −80° C. and thawing at 37° C., except for an initial freezing of 30 min. After 4^{th} freeze—thaw, cell debris was removed by centrifugation at 400×g for 5 minutes. Purified IgG preparations and cell lysates were then quantitated using a BCA protein assay (Pierce, Cat#23225) according to manufacturer's instructions. To create immune complexed stimulated conditioned media preparations, PBMCs from healthy donor sodium heparinized blood were isolated using Cell Preparation tubes (BD Vacutainer, Cat#362753), resuspended in RPMI 1640 (Life Technologies, Cat#11875-085) +10% FBS (Life Technologies, Cat#16140-063) media at 2×10^6 cells/ml and plated in 6 well plates in a volume of 2 ml/well. Purified IgG from SLE and healthy serum was premixed with cell lysates at equivalent concentrations of 500 ug/ml each and incubated at RT for 30 minutes and then added to PBMCs in a volume of 2 ml per well and incubated for 24 hours at 37° C. Plates were centrifuged at 1000 rpm for 5 minutes and PBMC immune complex-stimulated conditioned media was collected, aliquoted, and stored at −80° C. for future use.

Activity Assay

[0610] HEK-Blue IFNα/β cells (Invivogen) were plated in a 96 well flat bottom plate at 50,000 cells per well in 200 μl DMEM (Life Technologies) +10% fetal bovine serum (Life Technologies) and incubated for 5 hours at 37° C. to allow cells to adhere to plate. After 5 hours, Hek-Blue cells were removed from incubator and supernatants were replaced with a 1:6 dilution of donor 232 PBMC conditioned media or a 1:81 dilution of donor 293 conditioned media (using HEK-Blue cell culture media as a diluent) with or without the following treatments: broad anti-IFN-α antagonist mAb (M24, human IgG1) at 0.4, 2, 10, 50, and 100 μg/ml along with a fixed concentrations of 20 μg/mlisotype control (R&D Systems, murine IgG1), 100 μg/ml anti-IFN-α combined with 20 μg/ml anti-IFN-ω antagonist mAb (eBioscience, clone OMG5, murine IgG1), or 100 μg/ml human IgG1 isotype control (Southern Biotech) combined with 20 μg/ml murine IgG1 isotype control. Cells were incubated overnight at 37° C. The next day, 40 μl of cell supernatant from each well was removed and added to 160 μl of Quanti-Blue alkaline phosphatase substrate (Invivogen) in a separate 96 well flat bottom plate. Supernatants were allowed to react with the substrate for 10 minutes at which time the plate was read on a spectrophotometer at 650 nm wavelength. Optical densities were plotted in GraphPad Prism

[0611] The additional blockade of IFN-ω in the presence of INF-α antagonist resulted in enhanced suppression of SLE-relevant IFN-I activity than blockade of INF-α alone (FIG. **2**). As expected, conditioned media from PBMCs stimulated with immune complexes from healthy donor (HV IC Conditioned media) did not have detectable ISRE activity indicating the interferogenic potential of SLE patient immune complexes.

EXAMPLE 3

Immunomodulatory Effects Ef IFN-ω are Similar to those of IFN-α

[0612] Ability of IFN-ω to induce chemokine secretion, IFN gene signature, dendritic cell maturation and activation, and B-cell maturation was evaluated in comparison to IFN-α. In these studies, IFN-αA and IFN-α2, two of the most widely used therapeutic IFN-α molecules, were primarily used as representative INF-α subtype controls. In some assays, IFN-αB2 was used.

Induction of Chemokine Secretion and IFN Gene Signature

[0613] PBMCs isolated from 6 individual healthy human donors were stimulated with IFN-αA (IFN-α2) or IFN-ω, and the supernatants and pellets were collected for analyses. 3, 6 and 24 hours post-treatment. A panel of 25 cytokines were measured from the supernatants using Luminex immunoassay: IL-1β, IL-IRA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, TNFα, IFN-α, IFN-γ, GM-CSF, MIP-1α, MIP-1β, IP-10, MIG, Eotaxin, RANTES, and MCP-1. IFN-ω and IFN-α2 both enhanced the level of detectable IP-10, MCP-1, IL-IRA, IL-6, MIP-1α, and MIP-1β. FIG. **3** shows the induction of IP-10 by IFN-ω and IFN-α2. IL-8 secretion was reduced by both treatments in these experiments. IL-2R, IL-12 and RANTES levels were not altered by INF-α or IFN-ω treatment (with the exception of one donor which had an increase in RANTES only). All other analytes in the cytokine panel did not change with respect to INF-α or IFN-ω treatment or were below the limit of detection.

[0614] Collected pellets were processed for RNA and evaluated using a 21-gene IFN panel signature by microarray to evaluate possible similarities and/or differences in IFN-ω and INF-α induced expression. Human PBMCs treated with IFN-ω exhibited neary indistinguishable qualitative and kinetic gene expression responses as compared to IFN-αA-treated cells. 92.5% of genes modulated by IFN-αA treatment versus untreated control were also modulated by IFN-ω treatment at 3 h. At the 6 and 24 h post-treatment time points,

97.83% and 99.25% of genes modulated by INF-α treatment were also modulated by IFN-ω, respectively (data not shown).

[0615] In summary, INF-α and IFN-ω induced indistinguishable qualitative cytokine release and gene expression profiles between PBMC preparations obtained from 6 individual healthy human donors suggesting that they may confer similar immunomodulatory effects.

IFN-ω Induces Differentiation of Dendritic Cells which is Inhibited by IFN-ω Blocking Antibodies

[0616] Ability of IFN-ω and INF-α to induce monocyte to DC differentiation and the functionality was evaluated.

[0617] Purified monocytes were differentiated to DC in the presence of GM-CSF alone or with INF-α or IFN-ω in the presence or absence of 50 μg/ml anti-INF-α or anti-IFN-ω for 3 days using standard methods. Cells were harvested and analyzed for surface marker expression by 8-color FACS. Both INF-α and IFN-ω induced characteristic DC surface marker expression CD83, and CD80, CD86, CD40, CD11c, and reduced expression or monocyte marker CD14. Addition of either anti-INF-α or anti- IFN-ω at concentration 50 μg/ml at the beginning of culture partially inhibited DC differentiation while the isotype antibody had no effect (data not shown).

[0618] Mixed lymphocyte reaction (MLR) was used to demonstrate the functionality of the differentiated DCs. The differentiated DCs were harvested, washed, resuspended in fresh media, and cultured with purified CD4+ T cells at DC:$CD4^+$ T cell ratios of 1:10, 1:20, and 1:100. On day 6 supernatants were collected and analyzed for secreted cytokines using a multiplex beads assay for 26 cytokines/chemokines. DCs differentiated in the presence of either IFN-α or IFN-ω activated $CD4^+$ cells as shown by secretion of T cell specific cytokines IFN-γ and IL-17. DCs differentiated in the presence either the anti-IFN-α or the anti-IFN-ω antibody did not induce $CD4^+$ T cell activation. FIG. **4**A shows the lack of induced IFN-γ secretion from the CD4+ cells activated by DCs differentiated in the presence of anti-IFN-α or anti-IFN-ω antibodies. FIG. **4**B shows the lack of induced IL-17 secretion from the CD4+ cells activated by DCs differentiated in the presence of anti-INF-α or anti-IFN-ω antibodies. IFN-α and IFN-ω also induced secretion of IL-4, IL-5, IL-12p40 and IL-13 (data not shown). All culture conditions included GM-CSF. Data is representative of 2 studies. Error bars indicate SD of Luminex triplicates. In the experiment shown in the figure, data illustrated a DC to CD4 T cell ratio of 1:20 was used.

IFN-ω Induces T-Cell Independent B Cell Activation

[0619] B cells play a critically important role in lupus pathogenesis through the production of pathogenic autoantibodies and cytokines, and by presenting antigens to T cells. B cell activation and functional maturation can occur in a T cell-dependent (TD) or T cell-independent (TI) fashion. In TI B cell responses, B cells are released from T-dependent tolerance control as TLR ligands or dendritic cell-derived cytokines are able to substitute for T cell help. In SLE, where both TLR ligands (e.g. double-stranded DNA) and DC-derived cytokines (e.g. type I IFNs) are believed to contribute to disease pathogenesis, TI B cell activation represents a likely relevant mechanism. Besides the production of autoantibodies, autoreactive B cells are thought to play important pathogenic roles by presenting autoantigens to T cells and secreting pro-inflammatory cytokines. INF-α has been reported to enhance the production of pro-inflammatory IL-6 by human B cells activated with antibodies against the B cell receptor (BCR) and CpG (mimicking specific antigen and TLR-signals, respectively) in the absence of T cell-derived factors. Furthermore, co-culture with plasmacytoid DCs was shown to enhance B cell activation as determined by CD86 expression levels that was dependent on soluble factors. The ability of IFN-ω to enhance CD86-expression and pro-inflammatory cytokine production by human B cells was investigated using a T cell-independent culture system Peripheral blood B cells were cultured with CpG (ODN-2006), anti-BCR, and CpG & anti-BCR, and varying concentrations of IFN-α2 (Alpha 2b) or IFN-ω as indicated (IFN concentrations in U/ml). CD86-expression (median fluorescence levels) was determined after 3 days by flow cytometry, and supernatants were analyzed by 26-plex Luminex immunoassay, including IL-6. The results were expressed as mean values of duplicate samples±SD.

[0620] Dose-dependent IFN-ω-induced up-regulation of CD86 expression upon anti-BCR and anti-BCR/CpG stimulation was observed with both donor samples tested, whereas co-culture of B lymphocytes without stimulus showed only a weak effect. INF-ω induced CD86 expression to a similar extent than IFN-α2B. FIG. **5**A shows the IFN-ω-induced CD86 expression from B cells from one donor. IFN-ω also dose-dependently induced IL-6-production upon CpG and anti-BCR/CpG stimulation to similar extent than IFN-α2B with both donor samples tested. FIG. **5**B shows the IFN-ω-induced IL-6 secretion from B cells from one donor.

IFN-ω Induces BLyS Secretion

[0621] BLyS (BAFF) is a B cell survival factor and a clinically validated target in human SLE. INF-α treatment has been found to induce BLyS gene expression in vivo as determined by microarray and qPCR analysis of PBMCs isolated from patients 24 h after dosing. Ability of IFN-ω to induce secretion of BLyS was therefore assessed.

[0622] PBMCs were isolated from two different normal healthy donors. Equivalent concentrations of IFN-ω and INF-α were used to stimulate cells for 72 hours at which time supernatants were collected and analyzed by ELISA for soluble BLyS. Results were expressed as mean values of duplicate samples±SD.

[0623] IFN-ω and INF-α were similarly competent in inducing the secretion of BLyS in human PBMCs in vitro. Results from one donor are shown in FIG. **6**.

EXAMPLE 4

Generation of Human Type I IFN Antigens used for Immunization, Phage Panning, Antibody Characterization, and Crystallography Studies

[0624] 20 individual recombinant human type I IFN alphas shown in Table 4 were cloned and expressed in HEK 293 cells using standard methods using signal sequences, such as SEQ ID NOs: 21-25. The proteins are human unless otherwise stated. To improve expression level and solubility, a single amino acid mutant at position 80 of human IFN-ω, IFN-ω T80E was generated and expressed in HEK 293 cells. The T80E IFN-ω variant (SEQ ID NO: 2) had comparable activity to the wild type protein. IFN-αD and IFN-α1 differ by one amino acid at position 114 (valine vs alanine). Alpha A and Alpha 2 differ by one amino acid at position 23 (lysine in Alpha A vs. arginine in Alpha 2). Alpha 4 has two forms, 4a

and 4b that differ by two amino acids at position 51 (alanine in Alpha 4a and threonine in Alpha 4b) and 114 (glutamate in Alpha 4a vs valine in Alpha 4b). These variations are located outside the receptor binding region and do not affect activity. Antibodies were found to neutralize these pairs of variants (αD/α1, αA/α2 and α4a/α4b) equally well and subsequently in some experiments only one antigen of each pair was used.

TABLE 4

IFN Protein	Alternative Name	GenBank Accession Number Adopted	SEQ ID NO:
IFN-αA	IFN-α2a	V00549	5
IFN-αB2	IFN-α8	X03125	6
IFN-αC	IFN-α10	NM_002171.1	7
IFN-αD	Val114 IFN-α1	V00538	8
IFN-αF	IFN-α21	V00540	9
IFN-αG	IFN-α5	X02956	10
IFN-αH2	IFN-α14	X02959	11
IFN-αI	IFN-α17	V00532	12
IFN-αJ1	IFN-α7	X02960	13
IFN-αK	IFN-α6	X02958	14
IFN-α4b	IFN-α4	X02955	15
IFN-αWA	IFN-α16	X02957	16
IFN-α2	IFN-α2b	V00548, NM_00605.2	17
IFN-α1	Ala114 IFN-αD	J00210	18
IFN-α4a	IFN-αM1	NM_021068	19
IFN-β		V00534	20
IFN-ω		NM_002177.1	1
IFN-ω T80E			2
Chimp IFN-ω		XM_528554.1	3
Cyno IFN-ω		NA	4

EXAMPLE 5

Generation of Antibodies Binding to INF-α and IFN-ω

[0625] INF-α and IFN-ω-binding Fabs were selected from de novo pIX phage display libraries as described in Shi et al., J Mol Biol 397:385-96, 2010; Int. Pat. Publ. No. WO2009/085462; U.S. Pat. Publ. No. US2010/0021477). Briefly, the libraries were generated by diversifying human scaffolds where germline VH genes IGHV1-69*01, IGHV3-23*01, and IGHV5-51*01 were recombined with the human IGHJ-4 minigene via the H3 loop, and human germline VLkappa genes 012 (IGKV1-39*01), L6 (IGKV3-11*01), A27 (IGKV3-20*01), and B3 (IGKV4-1*01) were recombined with the IGKJ-1 minigene to assemble complete VH and VL domains. The positions in the heavy and light chain variable regions around H1, H2, L1, L2 and L3 loops corresponding to positions identified to be frequently in contact with protein and peptide antigens were chosen for diversification. Sequence diversity at selected positions was limited to residues occurring at each position in the IGHV or IGLV germline gene families of the respective IGHV or IGLV genes. Diversity at the H3 loop was generated by utilizing short to mid-sized synthetic loops of lengths 7-14 amino acids. The amino acid distribution at H3 was designed to mimic the observed variation of amino acids in human antibodies. Library design is detailed in Shi et al., J Mol Biol 397:385-96, 2010. The scaffolds utilized to generate libraries were named according to their human VH and VL germline gene origin. The three heavy chain libraries were combined with the four germline light chains or germline light chain libraries to generate 12 unique VH:VL combinations for panning experiments against INF-α and IFN-ω.

[0626] The libraries were panned against either biotinylated human IFN-α2 or biotinylated human IFN-αG. After three rounds of panning, a polyclonal phage ELISA using human IFN-α2, IFN-αG and cynomolgus IFN-ω as antigens was performed to detect the specific enrichment of individual panning experiments. The phage collected from those panning experiments which demonstrated enrichment for binders to IFN-α2, IFN-αG and IFN-ω were further screened with a monoclonal Fab ELISA in which Fab proteins expressed from individual Fab clones were used as binders. The Fab clones with binding signal to 20 nM biotinylated antigen three times higher than the negative control were selected for secondary Fab screening. Select Fabs were cloned into IgG1/κ background and characterized further using ProteOn and ISRE reporter gene assay. From these assays, mAb IFWM371 was selected for further engineering and affinity maturation.

[0627] Table 5 shows affinities (K_D) and IC_{50} values for IFWM371 as measured using ProteOn and ISRE reporter gene assay for various Type I IFNs as well as IFN-β. Except IFN-α1 (IFN-αD), IFWM371 bound to all human IFN-alpha proteins tested ranging from 179 pM-10 nM. The antibodies did not bind IFN-α1 (IFN-αD). The antibody bound also human, chimpanzee and cynomolgus IFN-ω but did not bind IFN-β. IFWM371 demonstrated neutralizing activity to all tested INF-α molecules except IFN-α1 (αD), which the antibody did not neutralize. IFWM371 contains the VH IFWH591 (SEQ ID NO: 28) and the VL PH9L4 (germline 012) (SEQ ID NO: 29.

TABLE 5

	K_D (pM)	IC_{50} (nM)
IFN-αA	813	8.4
IFN-αB2	1140	19.3
IFN-αC	1670	53.9
IFN-αD	NB	NN
IFN-αF	5310	16
IFN-αG	1110	12.9
IFN-αH2	179	9.6
IFN-αJ1	10800	35.7
IFN-αK	245	7.3
IFN-αWA	3180	74.2
IFN-α4a	5390	32.8
IFN-β	NB	NN
chimp IFN-ω	1080	
cyno IFN-ω	887	
human IFN-ω	ND	43.9

NB: no binding
ND: not done
NN: non-neutralizing

EXAMPLE 6

Crystal Structure of IFWM371 in Complex with IFN-ω T80E

[0628] In order to reveal the epitope and paratope, the structural basis for its broad binding specificity to INF-α subtypes and IFN-ω, and to provide support for engineering to improve affinity and specificity, the crystallography study of human IFN-ω T80E in complex with Fab of IFWM371 was performed.

[0629] His-tagged Fab IFWM371 (IgG1/kappa isotype) was cloned and expressed in HEK293 cells and purified using

affinity, ion exchange and size-exclusion chromatography. The Fab was received in 20 mM Tris pH 7.4, 50 mM NaCl. Human IFN-ω T80E variant (hereafter simply IFN-ω) with a C-terminal 6×His-Tag was expressed in HEK293 cells. The protein was received in 20 mM Tris, pH 7.4, 50 mM NaCL.

[0630] The complex was prepared by mixing of IFN-ω with Fab IFWM371 in molar ratio of 1.2:1.0 (excess IFN-ω), incubated at 4° C. overnight, and purified on Superdex 200 column equilibrated with 20 mm HEPES pH 7.5, 0.25 M NaCl, then concentrated to 9.96 mg/ml using Amicon-Ultra 10 kDa cutoff. Crystals suitable for X-diffraction were obtained from 20% PEG 3K, 0.2M ammonium phosphate dibasic with MMS seeding (Obmolova, G., Malia, T. J., Teplyakov, A., Sweet, R. & Gilliland, G. L. (2010). Promoting crystallization of antibody-antigen complexes via microseed matrix screening. *Acta Crystallogr D Biol Crystallogr* 66, 927-33.).

[0631] For X-ray data collection, one crystal of IFN-ω/Fab IFWM371 complex was soaked for a few seconds in the mother liquor (20% PEG 3350, 0.2 M $(NH_4)_2HPO_4$, pH 7.9) supplemented with 20% glycerol, and flash frozen in the stream of nitrogen at 100 K. X-ray diffraction data were collected using a Rigaku MicroMax™-007HF microfocus X-ray generator equipped with an Osmic™ VariMax™ confocal optics, Saturn 944 CCD detector, and an X-stream™ 2000 cryocooling system (Rigaku, TX). Diffraction intensities were detected over a 205° crystal rotation in quarter-degree images. The X-ray data were processed with the program XDS. X-ray data statistics are given in Table 6.

[0632] The structure of the IFN-ω/Fab IFM371 complex was solved by molecular replacement (MR) with Phaser. The search models for MR were the crystal structure of Fab 15 (PDB ID 3NA9; Luo, J., Obmolova, G., Huang, A., Strake, B., Teplyakov, A., Malia, T., Muzammil, S., Zhao, Y., Gilliland, G. L. & Feng, Y. (2010). Coevolution of antibody stability and Vkappa CDR-L3 canonical structure. *J Mol Biol* 402, 708-19) and IFN-α4A. However, an MR solution could not be obtained for IFN-ω due to severe inter-molecular clashes. Inspection of the electron density map phased with Fab IFWM371 alone showed the electron density for over half of the IFN-ω molecule is missing. However, the remaining part of the IFN-ω molecule was readily fit in the density. The structure was then refined with PHENIX and model adjustments were carried out using COOT.

TABLE 6

Crystal data	
Space group	C2
Unit cell dimensions	
a, b, c (Å)	153.84, 69.84, 54.69
α, β, γ (°)	90, 106.87, 90
Asymmetric unit content	1 complex
X-ray data	
Resolution (Å)	50-1.81 (1.85-1.81)*
Number of measured reflections	175,220 (1,217)
Number of unique reflections	43,466 (588)
Completeness (%)	85.20 (39.5)
R_{merge}	0.056 (0.321)
<I/σ>	16.1 (3.1)
B-factor (Wilson plot) (Å^2)	20.1
Refinement	
Resolution (Å)	30.6-1.81 (1.84-1.81)
Number of refls used in refinement	43,463 (1113)
Number of all atoms	4,594
Number of water molecules	481
Rcryst (%)	18.3 (25.9)
Rfree (%)	21.5 (38.1)
RMSD bond lengths (Å)	0.002
RMSD bond angles (°)	0.73
RMSD B-factor main-chain (Å^2)	5.6
Mean B-factor (Å^2)	26.0
Protein	23.2
Solvent	38.0
MolProbity [25]	
Clash score	6.8
Rotamer outliers (%)	1.2
Ramachandran favored (%)	98.5
Ramachandran outliers (%)	0.0
Cβ deviation >0.25 Å	0

*Values for high-resolution shell are in parentheses

[0633] The overall molecular structure of the IFN-ω/Fab IFWM371 complex is shown in FIG. **7**A. There was one complex in the asymmetric unit. The molecular model for the IFN-ω molecule included residues 23-39 and 119-153, corresponding to helical segment AB and helices D and E. Residue numbering is according to IFN-ω amino acid sequence shown in SEQ ID NO: 1. The helices A, B and C and the connecting loops were disordered. The Fab molecular model contained residues from 1 to 212 for the light chain (SEQ ID NO: 29) and from 1 to 222 for the heavy chain (SEQ ID NO: 28). The C-terminal 6×His tag, inter-chain disulfide bond and residues of 137-141 of the heavy chain were disordered. In addition, there were a number of water molecules at the antibody/antigen interface that formed an extensive H-bonding networks (FIG. **7**B).

[0634] The observed parts of IFN-ω molecule were nearly identical to the corresponding parts of full-length model of a published IFN-ω (PDB id 3se4, Ca rmsd of 0.54 A for 40 residues) and very similar to IFN-α2 with an average Ca rmsd of 0.42 Å (six IFN-α2 molecules, pdb code 1rh2) for about 40 Cα atoms. The model for IFN-ω in the IFN-ω/Fab IFWM371 contained only parts of helices C and D as well as connecting loop (loop AB). The other parts were absent in the electron density. Crystal packing analyses showed that there was not enough room for the missing helices. Careful analyses of the diffraction data indicated this was not an artifact due to abnormalities such as twinning or incorrect space group assignment. Thus, it was most likely that the IFN-ω protein had been cleaved during the crystallization process.

[0635] Fab IFWM371 recognized a conformational epitope that is composed of residues of the AB loop (between S25 and D35) and residues M146, and K150 of helix E (FIG. **8**A). The paratope is composed of residues from five CDRs except LCDR2. The paratope residues form a series of pockets into which dock the side chains of residues F27, L30, and R33 of the short AB helix of IFN-ω. FIG. **8**B shows the paratope residues in VL and VH of IFWM371. The antibody and antigen interactions appear to be mostly van der Waals (vdw) and hydrophobic packing as well as H bonds between the antibody and antigen. FIG. **8**C shows a 2D Interaction map between IFN-ω and IFWM371 interactions. In the figure, IFN-ω epitope residues are highlighted in grey, VL paratope residues are boxed, and VH paratope residues are circled. The figure demonstrates that most antigen/antibody interactions are formed by the three epitope residues F27, L30 and R33 of the IFN-ω AB helix. Thus, this region of IFN-ω constitutes the main part of the epitope. Another feature of

this complex is that water molecules appeared to play a significant role mediating antigen recognition. Three water clusters (WCs) were present at the interface. WC1 contributed to H bond interactions between HCDR3 and R34, F36 and E147 of IFN-ω. WC2 mediated VH/VL pairing and H bonding between Fv and the main epitope residues L30, R33 and its neighbors. WC3 water molecules were at the periphery of the interface, probably less important for the interactions.

[0636] IFWM371 strongly binds a number of INF-α subtypes and IFN-ω except IFN-αD or IFN-α1. IFWM371 does not bind IFN-β. The sequence alignment of IFNs is shown in FIG. **9**. The IFWM371 epitope residues are largely conserved among the subtypes, suggesting that the broad specificity of IFNM371 is a result of epitope conservation. IFN-αD or IFN-αl, however, to which IFWM371 does not bind to, contains S27 instead of F27, leading to a loss of the majority of hydrophobic contacts of F27 side chain. Since F27 is docked in a deep pocket formed by residues of HCDR2, HCDR3 and LCDR3, loss of the side chain contacts most likely accounts for the very low or no binding by IFN-αD and IFN-α1 proteins. This also suggests that F27 is one of the binding "hot spot" residues. P26 is a residue that is less well conserved. A His or Leu residue occupies this position in several INF-α subtypes. Because of the size and shape differences, this residue can significantly influence the local interactions between IFWM371 and IFN-α's with these mutations.

EXAMPLE 7

Alanine Scan of IFWM371

[0637] Alanine scan of IFWM371 heavy and light chain CDR residues was conducted to guide subsequent affinity-maturation efforts. All residues in the CDRs of both heavy and light chains were replaced with alanine except some low solvent exposure or non-solvent exposed residues. When native residues at CDRs were alanine, they were replaced with Tyrosine and/or Serine and/or Aspartic acid. One position with possible developability liabilities (W104 in IFWH591, SEQ ID NO 28) was replaced with Alanine, Tyrosine, Serine, and Aspartic acid. The mutated mAbs were transiently expressed in HEK 293 cells and cell supernatants were tested for binding activity to a panel of IFNs by ELISA. Two V_H mutants, IFWH591 R59A (SEQ ID NO: 30) and IFWH591 N103A (SEQ ID NO: 31), had significantly improved binding compared to the parent mAb.

EXAMPLE 8

Affinity-Maturation of IFWM371

Library Design

[0638] Two distinct V_L libraries (PH9L4L2 and PH9L4L3) were designed and used to affinity-mature IFWM371 light chain PH9L4 (O12) (SEQ ID NO: 29). The positions chosen for diversification of library PH9L4L2 were based on residue positions frequently found in anti-protein and anti-peptide complexes. The residues used to diversify each position were encoded within the germline gene family of IGKV genes (Shi et al (2010) J. Mol. Biol. 397:385-96). The library complexity was limited to not exceed 10^7 library members so that the diversity could be fully assessed during affinity maturation (the actual library complexity: 3.5^7). Table 7 shows the library design diversification scheme for LCDR1 position 30, 31 and 32, LCDR2 positions 50 and LCDR3 position 91, 92, 93, 94 and 96 of the V_L PH9L4 (012) in the library. Residue numbering is according to Kabat.

TABLE 7

Amino acid position on O12 (SEQ ID NO: 29)	Diversified with amino acid
Ser30	S, R, N, A, D
Ser31	N, S, K, D, G
Tyr32	Y, W, D, F, H, S, N, A, V
Ala50	A, D, G, K, Y, F, T, N
Ser91	Y, S, H, A
Tyr92	Y, N, D, S, H, I, F, K, G, R, E
Ser93	S, N, T, D, G, H, R
Thr94	T, Y, L, V, F, S, R, G, P, I
Leu96	W, Y, F, L, I, R, N

[0639] The residue positions to be diversified in the second light chain affinity-maturation library, PH9L4L3, were chosen based on analysis of structures between antibody-protein complexes and the diversity in each position was designed based on analyzing antibody protein structures as well as the amino acid usage in germline genes for each position (G. Raghunathan et al, Antigen-binding site anatomy and somatic mutations in antibodies that recognize different types of antigens. *J. Mol Recognit.* 25:103-113 (2012). For LCDR3, diversity was extended beyond natural repertoire to ensure that each position has amino acids of different biochemical properties (i.e., polar/nonpolar, positively/negatively charged). Additionally, the relative frequency of each amino acid per position were varied which was made possible using the Sloning library synthesis technology. Table 8 shows the library composition of PH9L4L3. Residue numbering is according to Kabat.

TABLE 8

Amino acid position on O12 (SEQ ID NO: 29)	Diversified with amino acid
Ser30	S, R, N, A, D
Ser31	N, S, T
Tyr32	Y, N, D, S, R
Tyr49	Y, K, E, H
Ala50	A, Y, W, S, G, N
Ser91	S, H, W, Y, E, A, G, D, N, R
Tyr92	Y, S, H, W, E, A, G, D, N, R
Ser93	S, H, W, Y, E, A, G, D, N, R
Thr94	T, S, H, W, Y, E, A, D, N, R, G
Leu96	W, Y, F, L, I

Panning and Characterization

[0640] Affinity maturation libraries were generated by combining the light chain libraries PH9L4L2 or PH9L4L3 with the parental heavy chain IFWH591 (SEQ ID NO: 28). The libraries were then used for panning to select for high affinity antibodies. Some affinity-maturation panning experi-

ments resulted in biased improvements in binding either only to IFN-ω or only to a few INF-α subtypes but not both. In order to generate broadly neutralizing antibodies with improved IC_{50} for most INF-α subtypes and IFN-ω, a subset of INF-α subtypes that were more diversified from each other (IFN-α2, IFN-α4a, IFN-αF and IFN-αG) were panned alternatively with cynomolgus monkey or human IFN-ω between each panning round. A total of three rounds of panning were carried out for each panning experiment.

[0641] Fab proteins of individual clones were expressed in TG-1 *E. coli* and bacterial cell lysates were used for Fab ELISAs to determine their affinities to human IFN-α4a, IFN-αF and IFN-ω compared to IFWM371. Since IFWM371 Fab bound these antigens weakly, Fab IFWF477 having higher affinity to the antigens was used as the surrogate Fab for comparison. 42 clones were identified that exhibited several folds higher binding activity than the surrogate Fab in ELISA. Some variants contained one amino acid insertion on LCDR1 which was not part of the original library design but was introduced during library synthesis. Overall, the affinity maturation of the V_L resulted in a significant improvement in binding compared to the surrogate Fab. The best clones from the two libraries showed over 23-fold higher binding activity to human IFN-ω than the surrogate Fab IFWF477 respectively.

[0642] For further functional and biophysical characterization, total of 42 light chains derived from the libraries were paired with the parental heavy chain IFWH591 (SEQ ID NO: 28) as well as two V_H variants with improved binding activity, IFWH624 (IFWH591 R59A, SEQ ID NO: 30) and IFWH629 (IFWH591 N103A, SEQ ID NO: 31), identified from the alanine scanning experiment described in Example 7. A total of 126 converted mAbs (42 light chains paired with three heavy chains) were then expressed and characterized further. Table 9 shows the parental and select affinity-matured antibodies and their heavy and light chain variable regions.

TABLE 9

Antibody name					
Protein cDNA name	Protein amino acid name	VL Peptide name	VH Peptide name	VH SEQ ID NO:	VL SEQ ID NO:
IFWM371	IFWB351	PH9L4	IFWH591	28	29
IFWM3301	IFWB3036	IFWL983	IFWH591	28	32
IFWM3302	IFWB3037	IFWL991	IFWH591	28	33
IFWM3303	IFWB3038	IFWL992	IFWH591	28	34
IFWM3304	IFWB3039	IFWL997	IFWH591	28	35
IFWM3305	IFWB3040	IFWL998	IFWH591	28	36
IFWM3291	IFWB3026	IFWL999	IFWH591	28	37
IFWM3306	IFWB3041	IFWL1000	IFWH591	28	38
IFWM3307	IFWB3042	IFWL1001	IFWH591	28	39
IFWM3308	IFWB3043	IFWL1004	IFWH591	28	40
IFWM3309	IFWB3044	IFWL1006	IFWH591	28	41
IFWM3310	IFWB3045	IFWL1007	IFWH591	28	42
IFWM3311	IFWB3046	IFWL1009	IFWH591	28	43
IFWM3312	IFWB3047	IFWL1010	IFWH591	28	44
IFWM3313	IFWB3048	IFWL1013	IFWH591	28	45
IFWM3314	IFWB3049	IFWL1014	IFWH591	28	46
IFWM3315	IFWB3050	IFWL1017	IFWH591	28	47
IFWM3316	IFWB3051	IFWL1022	IFWH591	28	48
IFWM3317	IFWB3052	IFWL1026	IFWH591	28	49
IFWM3318	IFWB3053	IFWL1038	IFWH591	28	50
IFWM3319	IFWB3054	IFWL1041	IFWH591	28	51
IFWM3320	IFWB3055	IFWL1047	IFWH591	28	52
IFWM3321	IFWB3056	IFWL1048	IFWH591	28	53
IFWM3322	IFWB3057	IFWL1051	IFWH591	28	54
IFWM3323	IFWB3058	IFWL1053	IFWH591	28	55

TABLE 9-continued

Antibody name					
Protein cDNA name	Protein amino acid name	VL Peptide name	VH Peptide name	VH SEQ ID NO:	VL SEQ ID NO:
IFWM3325	IFWB3060	IFWL1060	IFWH591	28	56
IFWM3327	IFWB3062	IFWL1063	IFWH591	28	57
IFWM3328	IFWB3063	IFWL1064	IFWH591	28	58
IFWM3329	IFWB3064	IFWL1067	IFWH591	28	59
IFWM3330	IFWB3065	IFWL1071	IFWH591	28	60
IFWM3331	IFWB3066	IFWL1073	IFWH591	28	61
IFWM3332	IFWB3067	IFWL1074	IFWH591	28	62
IFWM3333	IFWB3068	IFWL1076	IFWH591	28	63
IFWM3334	IFWB3069	IFWL1082	IFWH591	28	64
IFWM3335	IFWB3070	IFWL1084	IFWH591	28	65
IFWM3336	IFWB3071	IFWL1085	IFWH591	28	66
IFWM3337	IFWB3072	IFWL1087	IFWH591	28	67
IFWM3338	IFWB3073	IFWL1091	IFWH591	28	68
IFWM3339	IFWB3074	IFWL1093	IFWH591	28	69
IFWM3340	IFWB3075	IFWL983	IFWH624	30	32
IFWM3341	IFWB3076	IFWL991	IFWH624	30	33
IFWM3342	IFWB3077	IFWL992	IFWH624	30	34
IFWM3343	IFWB3078	IFWL997	IFWH624	30	35
IFWM3344	IFWB3079	IFWL998	IFWH624	30	36
IFWM3292	IFWB3027	IFWL999	IFWH624	30	37
IFWM3345	IFWB3080	IFWL1000	IFWH624	30	38
IFWM3346	IFWB3081	IFWL1001	IFWH624	30	39
IFWM3347	IFWB3082	IFWL1004	IFWH624	30	40
IFWM3348	IFWB3083	IFWL1006	IFWH624	30	41
IFWM3349	IFWB3084	IFWL1007	IFWH624	30	42
IFWM3350	IFWB3085	IFWL1009	IFWH624	30	43
IFWM3351	IFWB3086	IFWL1010	IFWH624	30	44
IFWM3352	IFWB3087	IFWL1013	IFWH624	30	45
IFWM3353	IFWB3088	IFWL1014	IFWH624	30	46
IFWM3354	IFWB3089	IFWL1017	IFWH624	30	47
IFWM3355	IFWB3090	IFWL1022	IFWH624	30	48
IFWM3356	IFWB3091	IFWL1026	IFWH624	30	49
IFWM3357	IFWB3092	IFWL1038	IFWH624	30	50
IFWM3358	IFWB3093	IFWL1041	IFWH624	30	51
IFWM3359	IFWB3094	IFWL1047	IFWH624	30	52
IFWM3360	IFWB3095	IFWL1048	IFWH624	30	53
IFWM3361	IFWB3096	IFWL1051	IFWH624	30	54
IFWM3364	IFWB3099	IFWL1060	IFWH624	30	56
IFWM3366	IFWB3101	IFWL1063	IFWH624	30	57
IFWM3367	IFWB3102	IFWL1064	IFWH624	30	58
IFWM3368	IFWB3103	IFWL1067	IFWH624	30	59
IFWM3369	IFWB3104	IFWL1071	IFWH624	30	60
IFWM3370	IFWB3105	IFWL1073	IFWH624	30	61
IFWM3371	IFWB3106	IFWL1074	IFWH624	30	62
IFWM3372	IFWB3107	IFWL1076	IFWH624	30	63
IFWM3374	IFWB3109	IFWL1084	IFWH624	30	65
IFWM3375	IFWB3110	IFWL1085	IFWH624	30	66
IFWM3376	IFWB3111	IFWL1087	IFWH624	30	67
IFWM3377	IFWB3112	IFWL1091	IFWH624	30	68
IFWM3378	IFWB3113	IFWL1093	IFWH624	30	69
IFWM3379	IFWB3114	IFWL983	IFWH629	31	32
IFWM3380	IFWB3115	IFWL991	IFWH629	31	33
IFWM3381	IFWB3116	IFWL992	IFWH629	31	34
IFWM3382	IFWB3117	IFWL997	IFWH629	31	35
IFWM3383	IFWB3118	IFWL998	IFWH629	31	36
IFWM3293	IFWB3028	IFWL999	IFWH629	31	37
IFWM3384	IFWB3119	IFWL1000	IFWH629	31	38
IFWM3385	IFWB3120	IFWL1001	IFWH629	31	39
IFWM3386	IFWB3121	IFWL1004	IFWH629	31	40
IFWM3387	IFWB3122	IFWL1006	IFWH629	31	41
IFWM3388	IFWB3123	IFWL1007	IFWH629	31	42
IFWM3389	IFWB3124	IFWL1009	IFWH629	31	43
IFWM3390	IFWB3125	IFWL1010	IFWH629	31	44
IFWM3391	IFWB3126	IFWL1013	IFWH629	31	45
IFWM3392	IFWB3127	IFWL1014	IFWH629	31	46
IFWM3393	IFWB3128	IFWL1017	IFWH629	31	47
IFWM3394	IFWB3129	IFWL1022	IFWH629	31	48
IFWM3395	IFWB3130	IFWL1026	IFWH629	31	49
IFWM3396	IFWB3131	IFWL1038	IFWH629	31	50
IFWM3397	IFWB3132	IFWL1041	IFWH629	31	51
IFWM3398	IFWB3133	IFWL1047	IFWH629	31	52

TABLE 9-continued

Antibody name					
Protein cDNA name	Protein amino acid name	VL Peptide name	VH Peptide name	VH SEQ ID NO:	VL SEQ ID NO:
IFWM3399	IFWB3134	IFWL1048	IFWH629	31	53
IFWM3400	IFWB3135	IFWL1051	IFWH629	31	54
IFWM3401	IFWB3136	IFWL1053	IFWH629	31	55
IFWM3403	IFWB3138	IFWL1060	IFWH629	31	56
IFWM3405	IFWB3140	IFWL1063	IFWH629	31	57
IFWM3406	IFWB3141	IFWL1064	IFWH629	31	58
IFWM3407	IFWB3142	IFWL1067	IFWH629	31	59
IFWM3408	IFWB3143	IFWL1071	IFWH629	31	60
IFWM3409	IFWB3144	IFWL1073	IFWH629	31	61
IFWM3410	IFWB3145	IFWL1074	IFWH629	31	62
IFWM3411	IFWB3146	IFWL1076	IFWH629	31	63
IFWM3413	IFWB3148	IFWL1084	IFWH629	31	65
IFWM3414	IFWB3149	IFWL1085	IFWH629	31	66
IFWM3415	IFWB3150	IFWL1087	IFWH629	31	67
IFWM3416	IFWB3151	IFWL1091	IFWH629	31	68
IFWM3417	IFWB3152	IFWL1093	IFWH629	31	69
IFWM3418	IFWB3153	IFWL1049	IFWH591	28	70
IFWM3419	IFWB3154	IFWL1049	IFWH629	31	70

TABLE 9-continued

Antibody name					
Protein cDNA name	Protein amino acid name	VL Peptide name	VH Peptide name	VH SEQ ID NO:	VL SEQ ID NO:
IFWM3420	IFWB3155	IFWL1049	IFWH624	30	70
IFWM3421	IFWB3156	IFWL984	IFWH591	28	71
IFWM3423	IFWB3158	IFWL984	IFWH629	31	71

[0643] Affinities of the 126 generated mAbs to a panel of human IFN-ω and human IFN-α subtypes were measured by ProteOn. The mAbs were transiently transfected in triplicate along with controls in HEK 293E cells in 48-well plates and cell supernatants were used in this experiment. To increase the assay throughput, only one concentration of the individual antigen was used. Table 10 shows the K_D values for the parental IFWM371 and select affinity-matured antibodies. Most of the mAbs showed significant improvement of binding affinity to all antigens tested. Some of them showed more than 100-fold improvement over the parental mAb.

TABLE 10

	K_D (pM)								
Protein cDNA name	IFN-ω	IFN-αC	IFN-αF	IFN-αJ1	IFN-α4a	IFN-αB2	IFN-αG	IFN-αWA	IFN-α2
IFWM371	1060	865	775	4230	4180	418	263	1390	116
IFWM3301	18	24	29	74	146	39	29	79	42
IFWM3302	52	83	72	231	268	54	98	168	250
IFWM3303	13	79	134	157	299	32	82	168	63
IFWM3304	32	26	32	53	120	40	37	92	23
IFWM3305	31	114	113	154	223	17	127	201	245
IFWM3291	28	45	51	122	317	60	67	125	82
IFWM3306	20	27	25	86	147	30	29	70	38
IFWM3307	46	62	55	305	426	55	58	162	132
IFWM3308	38	52	53	203	246	49	45	99	109
IFWM3309	55	109	140	275	383	41	120	139	96
IFWM3310	65	57	40	101	177	63	54	91	384
IFWM3311	12	36	21	56	223	16	56	72	134
IFWM3312	13	22	20	68	144	22	13	38	35
IFWM3313	56	74	84	221	354	74	118	155	295
IFWM3314	20	26	21	39	92	16	28	42	57
IFWM3315	63	59	50	134	240	92	61	115	192
IFWM3316	42	42	33	70	168	57	87	73	123
IFWM3317	16	133	121	206	370	11	126	162	223
IFWM3318	18	30	34	119	252	48	40	91	64
IFWM3319	34	52	44	151	274	76	49	107	152
IFWM3320	21	20	13	61	89	26	33	41	24
IFWM3321	33	33	24	79	159	45	36	58	90
IFWM3322	40	42	33	127	272	56	58	86	37
IFWM3323	73	77	48	144	337	77	94	121	104
IFWM3325	11	22	32	92	111	6	33	91	55
IFWM3327	39	34	35	113	164	60	35	106	60
IFWM3328	108	99	91	360	410	132	72	207	482
IFWM3329	59	50	51	166	258	95	61	173	532
IFWM3330	45	112	366	631	375	58	82	175	38
IFWM3331	15	12	13	72	85	21	15	26	33
IFWM3332	34	31	54	135	139	55	50	76	68
IFWM3333	53	65	89	607	477	137	77	258	457
IFWM3334	345	620	5210	2400	744	436	941	517	86
IFWM3335	42	49	61	245	336	111	77	137	151
IFWM3336	19	47	61	110	235	46	51	105	35
IFWM3337	20	17	16	71	91	22	34	37	43
IFWM3338	57	46	64	245	319	108	46	200	134
IFWM3339	49	59	65	161	235	94	79	141	115
IFWM3340	4	48	41	124	201	8	24	56	44
IFWM3341	8	104	88	275	445	7	63	134	151
IFWM3342	68	142	164	269	589	43	14	95	47
IFWM3343	20	65	63	157	237	60	60	83	106

TABLE 10-continued

Protein cDNA name	K_D (pM) IFN-ω	IFN-αC	IFN-αF	IFN-αJ1	IFN-α4a	IFN-αB2	IFN-αG	IFN-αWA	IFN-α2
IFWM3344	78	161	140	274	442	80	112	105	305
IFWM3292	18	123	98	295	613	21	49	72	254
IFWM3345	4	72	120	169	324	9	92	111	158
IFWM3346	52	105	117	505	480	44	86	170	183
IFWM3347	48	96	136	411	350	41	84	125	347
IFWM3348	50	83	64	164	89	58	20	49	42
IFWM3349	7	56	52	123	174	8	65	102	291
IFWM3350	20	57	54	55	161	33	98	66	366
IFWM3351	4	48	53	140	113	10	15	33	30
IFWM3352	60	121	152	287	267	48	90	87	193
IFWM3353	6	54	55	95	110	6	16	31	90
IFWM3354	17	43	32	98	123	23	43	52	360
IFWM3355	26	55	52	79	122	39	60	41	212
IFWM3356	274								
IFWM3357	4	23	39	130	170	8	14	37	8
IFWM3358	18	54	47	223	319	62	48	123	103
IFWM3359	21	41	53	136	147	34	40	51	152
IFWM3360	25	56	49	174	233	35	43	61	236
IFWM3361	30	101	135	388	622	48	66	98	151
IFWM3364	13	93	109	254	269	39	80	118	151
IFWM3366	21	30	27	109	122	40	30	66	433
IFWM3367	57	116	100	453	465	86	67	152	42735
IFWM3368	28	62	59	181	203	62	48	103	47393
IFWM3369	81	88	190	622	344	123	121	220	58
IFWM3370	10	39	39	225	155	24	21	41	42
IFWM3371	18	43	50	125	100	23	50	64	81
IFWM3372	49	94	116	690	432	154	103	272	717
IFWM3374	55	106	121	568	540	139	96	208	349
IFWM3375	19	22	23	45	67	33	35	31	27
IFWM3376	20	34	39	140	113	37	48	62	81
IFWM3377	27	44	51	192	193	58	38	120	132
IFWM3378	75	172	168	496	533	141	150	248	279
IFWM3379	15	13	13	33	72	22	13	23	27
IFWM3380	25	46	32	76	88	14	70	59	157
IFWM3381	45	79	92	121	171	58	53	67	37
IFWM3382	30	24	20	37	75	27	30	32	18
IFWM3383	28	69	60	86	143	33	84	64	194
IFWM3293	29	25	17	62	166	12	37	46	120
IFWM3384	26	29	33	68	77	13	22	17	25
IFWM3385	32	41	41	142	178	19	23	52	42
IFWM3386	26	31	29	87	103	16	26	35	43
IFWM3387	39	90	58	161	169	36	34	69	19
IFWM3388	33	30	19	55	84	26	27	44	105
IFWM3389	17	24	9	32	98	10	33	30	69
IFWM3390	10	11	11	30	75	14	10	29	26
IFWM3391	23	16	25	66	117	29	44	42	63
IFWM3392	23	16	14	21	58	34	19	25	44
IFWM3393	57	49	41	96	166	70	64	78	284
IFWM3394	45	63	63	77	105	123	91	49	304
IFWM3395	19	116	102	181	279	3	63	63	83
IFWM3396	11	5	7	37	79	48	61	68	52
IFWM3397	25	27	28	78	119	42	43	62	103
IFWM3398	26	17	17	44	61	32	22	30	34
IFWM3399	30	25	21	50	88	36	30	37	59
IFWM3400	33	23	22	60	135	32	52	49	68
IFWM3401	62	42	28	78	195	42	67	76	604
IFWM3403	7	25	27	59	62	8	27	23	11
IFWM3405	20	22	19	36	67	17	15	39	38
IFWM3406	78	37	37	119	135	39	37	63	34
IFWM3407	17	32	33	58	128	13	27	60	65
IFWM3408	86	730	5690	1870	703	54	895	176	17
IFWM3409	14	11	9	41	58	18	5	25	28
IFWM3410	29	37	52	82	86	59	52	52	33
IFWM3411	28	23	37	151	101	53	35	87	53
IFWM3413	47	37	33	150	206	58	44	85	121
IFWM3414	58	68	101	174	193	13	33	70	26
IFWM3415	18	19	26	51	69	15	26	44	39
IFWM3416	28	29	45	68	103	37	29	69	55
IFWM3417	29	31	39	70	100	36	30	59	41
IFWM3418	89	191	229	656	1160	206	178	493	208

TABLE 10-continued

Protein cDNA name	K_D (pM) IFN-ω	IFN-αC	IFN-αF	IFN-αJ1	IFN-α4a	IFN-αB2	IFN-αG	IFN-αWA	IFN-α2
IFWM3419	86	126	158	399	582	90	81	193	87
IFWM3420	36	113	118	299	475	61	37	124	35

[0644] Select antibodies from the panel of 126 were characterized in an ISRE assay for their ability to inhibit a spectrum of INF-α subtypes and IFN-ω, and their solubility and biophysical characteristics were assessed. IC_{50} values from the ISRE assay are shown in Table 11 and Table 12 for select antibodies. The IC_{50} values were at double-digit pM or lower for several antibodies to 11 recombinant INF-α subtypes and to IFN-ω. This represents more than a hundred-fold improvement over the parental mAb, IFWM371, whose IC_{50} against its antigens ranging from single digit to double digit nM. As the parental antibody, the affinity-matured antibodies did not neutralize IFN-αD or IFN-β.

[0645] The most potent affinity-matured antibody mAb IFWM3423 had almost a single-digit picomolar IC_{50} to all interferon subtypes it bound.

TABLE 11

mAbs	IC_{50} (pM) αA	αB2	αC	αD	αF	αG	αH2
IFWM371	8400	19300	53900	NN	16000	12900	9600
IFWM3304	29	39	117	NN	62	47	42
IFWM3307	73	247	583	NN	170	95	88
IFWM3308	94	230	996	NT	155	167	32
IFWM3310	50	43	196	NN	111	73	45
IFWM3314	29	33	157	NN	58	57	40
IFWM3320	45	18	392	NT	54	82	23
IFWM3321	29	87	266	NN	54	34	28
IFWM3322	31	121	306	NN	117	83	46
IFWM3328	216	520	1416	NN	631	486	440
IFWM3331	18	80	98	NN	48	27	33
IFWM3332	104	327	479	NN	228	99	92
IFWM3385	63	158	272	NN	66	77	29
IFWM3399	43	62	189	NN	29	29	13
IFWM3400	35	86	138	NN	43	35	15
IFWM3405	40	99	68	NN	35	26	16
IFWM3410	NT	211	168	NN	77	55	33
IFWM3416	81	250	112	NN	64	49	35
IFWM3421	13	16	20	NN	11	18	8
IFWM3423	12	11	12	NN	8	9	4

NN: not neutralizing;
NT: not tested

TABLE 12

mAbs	IC_{50} (pM) αI	αJ1	αK	αWA	α4a	IFN-β	IFN-ω
IFWM371		35700	7300	74200	32800	NN	43900
IFWM3304	157	126	57	237	112	NN	31
IFWM3307	752	328	95	600	501	NN	100
IFWM3308	478	363	59	894	295	NN	40
IFWM3310	258	166	96	473	169	NN	81
IFWM3314	163	86	65	188	137	NN	32
IFWM3320	355	213	34	633	166	NN	53
IFWM3321	301	114	46	267	295	NN	38

TABLE 12-continued

mAbs	IC_{50} (pM) αI	αJ1	αK	αWA	α4a	IFN-β	IFN-ω
IFWM3322	460	169	71	382	352	NN	59
IFWM3328	2002	1657	321	3078	1169	NN	456
IFWM3331	198	94	28	109	117	NN	50
IFWM3332	893	487	76	947	519	NN	228
IFWM3385	225	251	65	839	414	NN	68
IFWM3399	18	106	32	189	111	NN	27
IFWM3400	137	154	35	376	220	NN	29
IFWM3405	72	26	22	216	86	NN	19
IFWM3410	183	217	41	538	192	NN	89
IFWM3416	158	61	43	779	201	NN	40
IFWM3421	17	14	18	14	15	NN	8
IFWM3423	4	6	9	10	8	NN	6

NN = not neutralizing

EXAMPLE 9

Engineering of Antibodies to Minimize Post-Translational Modification Risk

[0646] Based on neutralizing activity, solubility and biophysical properties, four mAbs derived from affinity maturation of IFWM371, IFWM3331 (IFWB3066), IFWM3399 (IFWB3134), IFWM3421 (IFWB3156) and IFWM3423 (IFWB3158) were analyzed further. The heavy chains of these mAbs consist of either IFWH591 (SEQ ID NO: 28) or IFWH629 (SEQ ID NO: 31) and the light chains of them consist of either IFWL984 (SEQ ID NO: 71) or IFWL1048 (SEQ ID NO: 53) or IFWL1073 (SEQ ID NO: 61).

[0647] Both VH chains contain several potential post-translational modification (PTM) motifs in their CDRs, including an acid-catalyzed hydrolysis sequence motif (D52-P53), an isomerization motif (D55-556) on HCDR2 and potential oxidation sites on HCDR1 (W33) and CDR-H3 (W104).

[0648] The VL of IFWL984 (SEQ ID NO: 71) and IFWL1048 (SEQ ID NO: 53) contain one isomerization motif (D30-G31) on LCDR1 while the VL of IFW1073 (SEQ ID NO: 61) contains potential oxidation sites on LCDR3 (W92 and W94) and a potential deamidation site on LCDR1 (N31-532).

[0649] To reduce PTM risks on heavy chain CDRs, D52 in HCDR2 was back-mutated to the germline residue tyrosine (D52Y). P53 was mutated to Alanine. W104 in HCDR3 (VH_W 104) was replaced with alanine, tyrosine, serine or aspartic acid. The mutated heavy chains were co-expressed with three different light chains and tested in the ISRE assay. From these experiments, antibodies with heavy chain IFWH615 (SEQ ID NO: 157) and IFWH617 (SEQ ID NO: 158) were characterized further.

[0650] To reduce PTM risks on VL IFWL984 (SEQ ID NO: 71) and IFWL1048 (SEQ ID NO: 53), a series of mutations to

remove the potential PTM motifs were designed with the guidance of the structural information obtained from the IFWM371/IFN-ω complex structure described in Example 6. In addition, to improve the solubility of IFWM3421 (IFWB3156) and IFWM3423 (IFWB3158) having the common light chain IFWL984, a series of mutations on several hydrophobic residues in their CDRs were made to decrease the overall surface hydrophobicity of the antibody light chains. The IFWL984 variants were expressed in HEK293E cells with the parental heavy chain IFWH591 and the expressed antibody in cell supernatants were screened in the ISRE reporter gene assay for inhibition of IFN-ω and leukocyte IFN using methods described in example 11. The resulting antibodies IFWB3196 (D30E F32Y), IFWB3201 (D30S, G31S), and IFWB3202 (D30S, G31 S, F32Y) retained good neutralizing activity. Table 13 shows the VL sequences of the generated antibodies having the parental IFWH591 heavy chain variable region (SEQ ID NO: 28) and a variant IFWL984 light chain. The parental IFWM3421 has the IFWH591 VH and the parental IFWM3423 has the IFWH629 VH. Table 14 shows the IC_{50} values for neutralization of IFN-ω and leukocyte IFN of select generated antibodies.

TABLE 13

Antibody DNA ID	Antibody AA ID	VL Peptide ID	VL substitution	VL SEQ ID NO:
IFWM3421	IFWB3156	IFWL984	Parent control	71
IFWM3423	IFWB3158	IFWL984	Parent control	71
IFWM3454	IFWB3189	IFWL1112	IFWL984 D30S	123
IFWM3514	IFWB3248	IFWL1113	IFWL984 D30E	124
IFWM3455	IFWB3190	IFWL1114	IFWL984 F32Y	125
IFWM3456	IFWB3191	IFWL1115	IFWL984 F50A	126
IFWM3458	IFWB3193	IFWL1117	IFWL984 F50I	127
IFWM3459	IFWB3194	IFWL1118	IFWL984 F50L	128
IFWM3460	IFWB3195	IFWL1119	IFWL984 F50V	129
IFWM3461	IFWB3196[i]	IFWL1120	IFWL984 D30E, F32Y	130
IFWM3462	IFWB3197	IFWL1121	IFWL984 D30E, F50A	131
IFWM3463	IFWB3198	IFWL1122	IFWL984 D30E, F50I	132
IFWM3464	IFWB3199	IFWL1123	IFWL984 D30E, F50L	133
IFWM3465	IFWB3200	IFWL1124	IFWL984 D30E, F50V	134
IFWM3466	IFWB3201	IFWL1125	IFWL984 D30S, G31S	135
IFWM3467	IFWB3202	IFWL1126	IFWL984 D30S, G31S, F32Y	136
IFWM3470	IFWB3205	IFWL1129	IFWL984 D30G, G31D, F50Y	137
		IFWL1173	IFWL984 D30E, F32Y, F50Y	138
IFWM3526	IFWB3251	IFWL1174	IFWL984 D30E, F50Y	139
		IFWL1175	IFWL984 D30S, G31S, F50Y	140

TABLE 14

Antibody DNA ID	Antibody AA ID	IC_{50} (pM) human IFN-ω	IC_{50} (pM) Leukocyte IFN
IFWM3421	IFWB3156	7.4	0.7
IFWM3423	IFWB3158	10.7	1.1
IFWM3454	IFWB3189	11.2	1.3
IFWM3514	IFWB3248	10.4	1.4
IFWM3455	IFWB3190	24	not fitted
IFWM3456	IFWB3191	100.3	22.6
IFWM3458	IFWB3193	37	2.1
IFWM3459	IFWB3194	1518.9	4.4
IFWM3460	IFWB3195	43.5	not fitted
IFWM3461	IFWB3196[i]	21	1
IFWM3462	IFWB3197	41.6	12.6
IFWM3463	IFWB3198	41.4	6.6
IFWM3464	IFWB3199	46.8	5.6
IFWM3465	IFWB3200	33.7	1.7
IFWM3466	IFWB3201	10.3	0.9
IFWM3467	IFWB3202	51.8	0.8
IFWM3470	IFWB3205	52.3	7.4

[0651] Similarly, 26 IFWL1048 variants were constructed to reduce the PTM risks. The generated light chains were co-expressed with a heavy chain IFWH591 in HEK293E cells and the supernatant containing the antibody screened with ISRE assay. Table 15 shows the VH and VL sequences of the generated antibodies, and Table 16 shows the IC_{50} values of the antibodies for IFN-ω and leukocyte IFN. The resulting antibodies with variant IFWL1048 chains where the DG motif (D30-G31) in LCDR1 was eliminated, including IFWB3210 (D30S), IFWB3211 (D30E) and IFWB3223 (D30S, G31S), showed similar neutralization activity as the parent mAbs, IFWB3056 (VL: IFWL1048, VH: IFWH591) and IFWB3134 (VL: IFWL1048; VH: IFWH629). However, resulting antibodies with variant IFWL1048 chains with the DG motif eliminated and substitutions made to reduce hydrophobicity, including IFWB3219 (D30E, A32Y), IFWB3227 (D30S, G31S, F94L) and IFWB3230 (D30S, G31 S, A32Y, F94L) demonstrated a lower activity than the parental mAbs.

TABLE 15

Antibody DNA ID	Antibody AA ID	VL Peptide ID	Mutation	VL SEQ ID NO:
IFWM3321	IFWB3056	IFWL1048	Parent control	53
IFWM3399	IFWB3134	IFWL1048	Parent control	53
IFWM3475	IFWB3210	IFWL1135	IFWL1048 D30S	141
IFWM3476	IFWB3211	IFWL1136	IFWL1048 D30E	73
IFWM3477	IFWB3212	IFWL1137	IFWL1048 A32Y	142

TABLE 15-continued

Antibody DNA ID	Antibody AA ID	VL Peptide ID	Mutation	VL SEQ ID NO:
IFWM3483	IFWB3218	IFWL1143	IFWL1048 F94L	143
IFWM3484	IFWB3219	IFWL1144	IFWL1048 D30E, A32Y	74
IFWM3488	IFWB3223	IFWL1148	IFWL1048 D30S, G31S	75
IFWM3489	IFWB3224	IFWL1149	IFWL1048 D30S, G31S, A32Y	144

TABLE 15-continued

Antibody DNA ID	Antibody AA ID	VL Peptide ID	Mutation	VL SEQ ID NO:
IFWM3492	IFWB3227	IFWL1152	IFWL1048 D30S, G31S, F94L	145
IFWM3495	IFWB3230	IFWL1155	IFWL1048 D30S, G31S, A32Y, F94L	146
		IFWL1161	IFWL1048 D30G, G31D, A32F, F50A, F94L	147

TABLE 16

		IC_{50} (pM)	
Antibody DNA ID	Antibody AA ID	human IFN-ω	Leukocyte IFN
IFWM3321	IFWB3056	25.8	1.2
IFWM3399	IFWB3134	28.7	1.3
IFWM3475	IFWB3210	27.3	1.5
IFWM3476	IFWB3211	17.2	3.3
IFWM3477	IFWB3212	31	4.1
IFWM3483	IFWB3218	51.4	4.8
IFWM3484	IFWB3219	38.7	2.3
IFWM3488	IFWB3223	29.4	1
IFWM3489	IFWB3224	80.3	3.4
IFWM3492	IFWB3227	56.1	0.5
IFWM3495	IFWB3230	57.5	3.9

[0652] Potential PTM motifs on the VL IFWL1073 of IFWB3066 included potential oxidation sites on LCDR3 (W92 and W94). The LCDR3 of IFWL1073 (QQGWDWPLT; SEQ ID NO: 98) was replaced with a consensus LCDR3 sequence identified present in the LCDR3 of many affinity-matured antibodies (QQSYDFPLT; SEQ ID NO: 154). In addition, several mutants were designed to address a potential deamidation site (N31-S32) on LCDR1. 14 generated variants of IFWL1073 were paired with IFWH591 and expressed in 48-well HEK293E transient transfection. The cell supernatants were tested directly in ISRE assay for their neutralization activities against recombinant human IFN-ω and viral-induced leukocytes expressed IFNs. The mAbs with mutations W93Y and/or W95F showed some improvements in neutralization activity. Mutants to remove the NS motif by substitution or by shortening CDR-L1 showed reduction or loss of neutralization activity. Table 17 shows the VH and the VL sequences of the generated antibodies and Table 18 shows the IC_{50} values for IFN-ω and leukocyte IFN.

TABLE 17

Antibody DNA ID	Antibody AA ID	VL Peptide ID	VL Mutation	VL SEQ ID NO:
IFWM3331	IFWB3066	IFWL1073	Parent control	61
IFWM3501	IFWB3236	IFWL1162	IFWL1073 W93Y	148
IFWM3502	IFWB3237	IFWL1163	IFWL1073 W95F	149
IFWM3503	IFWB3238	IFWL1164	IFWL1073 W93Y, W95F	150
IFWM3527	IFWB3252	IFWL1176	IFWL1073 N31Q, W93Y, W95F	151
IFWM3528	IFWB3253	IFWL1177	IFWL1073 N31T, W93Y, W95F	152
IFWM3529	IFWB3254	IFWL1178	IFWL1073 S32T, W93Y, W95F	153

TABLE 18

		IC 50 (pM)	
Antibody DNA ID	Antibody AA ID	human IFN-ω	Leukocyte IFN
IFWM3331	IFWB3066	40.7	1.5
IFWM3501	IFWB3236	15.1	2.6
IFWM3502	IFWB3237	28	2.5
IFWM3503	IFWB3238	12	2.1

[0653] Select VL variants derived from the engineering efforts to minimize the PTM risk were paired with either IFWH591 or IFWH629 and scaled up for expression and purification. Table 19 shows the VL/VH pairing of the antibodies. Table 20 shows the IC_{50} values of the select resulting antibodies for various recombinant INF-α subtypes and IFN-ω.

TABLE 19

	VL			HC	
Antibody	Peptide ID	VL SEQ ID NO:	Description	Peptide ID	VH SEQ ID NO:
IFWL1073 mutants	IFWL1073	61	parent	IFWH591	28
	IFWL1164	150	IFWL1073 W93Y, W95F	IFWH591	28
	IFWL1176	151	IFWL1073 N31Q, W93Y, W95F	IFWH591	28
	IFWL1177	152	IFWL1073 N31T, W93Y, W95F	IFWH591	28
IFWL984 mutants	IFWL984	71	parent	IFWH591	28
	IFWL984	71	parent	IFWH629	31
	IFWL984	71	parent	IFWH629	31
	IFWL1125	135	IFWL984 D30S, G31S	IFWH591	28

TABLE 19-continued

	VL			HC	
Antibody	Peptide ID	VL SEQ ID NO:	Description	Peptide ID	VH SEQ ID NO:
	IFWL1126	136	IFWL984 D30S, G31S, F32Y	IFWH591	28
	IFWL1174	139	IFWL984 D30E, F50Y	IFWH591	28
	IFWL1048	53	parent	IFWH591	28
	IFWL1048	53		IFWH629	31
	IFWL1136	73	IFWL1048 D30E	IFWH591	28
	IFWL1148	75	IFWL1048 D30S, G31S	IFWH591	28

TABLE 20

Protein	Protein AA	(IC_{50} (pM)						
DNA ID	ID	αA	αB2	αC	αF	αG	α4a	ω
IFWM3331*	IFWB3066	26	77	48	157	33		52
		31	65	88	30	23		30
IFWM3421*	IFWB3156	16	19	29	16	18	22	8
		17	19	28	15	14	19	9
IFWM3423*	IFWB3158	20	17	24	21	20	23	16
		12	13	17	11	10	9	7
IFWM3466	IFWB3201	17	21	31	18	16	23	12
IFWM3503	IFWB3238	15	19	20	20	15	32	13
IFWM3399	IFWB3134	24	38	64	29	24	117	25
IFWM3476	IFWB3211	35	54	115	50	39	130	23
IFWM3488	IFWB3223	19	31	72	25	21	84	22

*results from two independent experiments

EXAMPLE 10

Broad Neutralizing Ability of Anti-IFN-α/ω Antibodies

[0654] Several of the generated antibodies neutralized IFN-ω and multiple INF-α subtypes with an IC_{50} of 100 pM or less, measured using the ISRE assay described above. The variable region sequences of these antibodies are shown in Table 21. Table 22 shows the LCDR1 sequences, Table 23 the LCDR2, Table 24 the LCDR3, Table 25 the HCDR1, Table 26 the HCDR2 and Table 27 the HCDR3 of the antibodies. FIG. **10** shows the IC_{50} values for each Type I IFN in the ISRE assay.

TABLE 21

mAbs cDNA	mAb protein	VH	VH SEQ ID NO:	VL	VL SEQ ID NO:
IFWM3308	IFWB3043	IFWH591	28	IFWL1004	40
IFWM3307	IFWB3042	IFWH591	28	IFWL1001	39
IFWM3410	IFWB3145	IFWH629	31	IFWL1074	62
IFWM3322	IFWB3057	IFWH591	28	IFWL1051	54
IFWM3385	IFWB3120	IFWH629	31	IFWL1001	39
IFWM3416	IFWB3151	IFWH629	31	IFWL1091	68
IFWM3310	IFWB3045	IFWH591	28	IFWL1007	42
IFWM3400	IFWB3135	IFWH629	31	IFWL1051	54
IFWM3321	IFWB3056	IFWH591	28	IFWL1048	53
IFWM3522	IFWB3211	IFWH591	28	IFWL1136	73
IFWM3524	IFWB3223	IFWH591	28	IFWL1148	75

TABLE 21-continued

mAbs cDNA	mAb protein	VH	VH SEQ ID NO:	VL	VL SEQ ID NO:
IFWM3320	IFWB3055	IFWH591	28	IFWL1047	52
IFWM3304	IFWB3039	IFWH591	28	IFWL997	35
IFWM3520	IFWB3201	IFWH591	28	IFWL1125	135
IFWM3399	IFWB3134	IFWH629	31	IFWL1048	53
IFWM3314	IFWB3049	IFWH591	28	IFWL1014	46
IFWM3331	IFWB3066	IFWH591	28	IFWL1073	61
IFWM3405	IFWB3140	IFWH629	31	IFWL1063	57
IFWM3442	IFWB3177	IFWH615	157	IFWL984	71
IFWM3525	IFWB3238	IFWH591	28	IFWL1164	150
IFWM3423	IFWB3158	IFWH629	31	IFWL984	71
IFWM3444	IFWB3179	IFWH617	158	IFWL984	71
IFWM3421	IFWB3156	IFWH591	28	IFWL984	71

TABLE 22

	LCDR1							
mAbs	Sequence							SEQ ID NO:
IFWM3308	Q	S	I	A	E	F		77
IFWM3307	Q	S	I	G	D	F		85
IFWM3410	Q	S	I	A	N	T	N	79
IFWM3322	Q	S	I	A	D	F		76
IFWM3385	Q	S	I	G	D	F		85
IFWM3416	Q	S	I	R	N	T	N	89
IFWM3310	Q	S	I	G	K	S		86
IFWM3400	Q	S	I	A	D	F		76
IFWM3321	Q	S	I	D	G	A		80
IFWM3522	Q	S	I	E	G	A		84
IFWM3524	Q	S	I	S	S	A		90
IFWM3320	Q	S	I	N	G	V		88
IFWM3304	Q	S	I	G	S	A		87
IFWM3520	Q	S	I	S	S	F		91
IFWM3399	Q	S	I	D	G	A		80
IFWM3314	Q	S	I	D	R	A		83
IFWM3331	Q	S	I	D	N	S	Y	82
IFWM3405	Q	S	I	A	N	N	N	78
IFWM3442	Q	S	I	D	G	F		81
IFWM3525	Q	S	I	D	N	S	Y	82
IFWM3423	Q	S	I	D	G	F		81
IFWM3444	Q	S	I	D	G	F		81
IFWM3421	Q	S	I	D	G	F		81

TABLE 23

	LCDR2			
mAbs	Sequence			SEQ ID NO:
IFWM3308	F	A	S	93
IFWM3307	F	A	S	93
IFWM3410	W	A	S	95
IFWM3322	F	A	S	93
IFWM3385	F	A	S	93
IFWM3416	W	A	S	95
IFWM3310	F	A	S	93
IFWM3400	F	A	S	93
IFWM3321	F	A	S	93
IFWM3522	F	A	S	93
IFWM3524	F	A	S	93
IFWM3320	F	A	S	93
IFWM3304	F	A	S	93
IFWM3520	F	A	S	93
IFWM3399	F	A	S	93
IFWM3314	F	A	S	93
IFWM3331	G	A	S	94
IFWM3405	W	A	S	95
IFWM3442	F	A	S	93

TABLE 23-continued

	LCDR2			
mAbs	Sequence			SEQ ID NO:
IFWM3525	G	A	S	94
IFWM3423	F	A	S	93
IFWM3444	F	A	S	93
IFWM3421	F	A	S	93

TABLE 24

	LCDR3									
mAbs	Sequence									SEQ ID NO:
IFWM3308	Q	Q	S	I	D	F	P	L	T	104
IFWM3307	Q	Q	A	L	D	F	P	L	T	96
IFWM3410	Q	Q	W	Y	D	N	P	L	T	107
IFWM3322	Q	Q	S	H	S	F	P	L	T	103
IFWM3385	Q	Q	A	L	D	F	P	L	T	96
IFWM3416	Q	Q	G	Y	D	T	P	F	T	100
IFWM3310	Q	Q	S	Y	D	F	P	L	T	105
IFWM3400	Q	Q	S	H	S	F	P	L	T	103
IFWM3321	Q	Q	A	Y	D	F	P	L	T	97
IFWM3522	Q	Q	A	Y	D	F	P	L	T	97
IFWM3524	Q	Q	A	Y	D	F	P	L	T	97
IFWM3320	Q	Q	S	H	D	F	P	L	T	102
IFWM3304	Q	Q	S	Y	D	F	P	L	T	105
IFWM3520	Q	Q	S	Y	D	L	P	I	T	106
IFWM3399	Q	Q	A	Y	D	F	P	L	T	97
IFWM3314	Q	Q	S	F	D	F	P	L	T	101
IFWM3331	Q	Q	G	W	D	W	P	L	T	98
IFWM3405	Q	Q	G	Y	D	T	P	F	T	100
IFWM3442	Q	Q	S	Y	D	L	P	I	T	106
IFWM3525	Q	Q	G	Y	D	F	P	L	T	99
IFWM3423	Q	Q	S	Y	D	L	P	I	T	106
IFWM3444	Q	Q	S	Y	D	L	P	I	T	106
IFWM3421	Q	Q	S	Y	D	L	P	I	T	106

TABLE 25

	HCDR1								
mAbs	Sequence								SEQ ID NO:
IFWM3308	G	Y	S	F	T	S	Y	W	109
IFWM3307	G	Y	S	F	T	S	Y	W	109
IFWM3410	G	Y	S	F	T	S	Y	W	109
IFWM3322	G	Y	S	F	T	S	Y	W	109
IFWM3385	G	Y	S	F	T	S	Y	W	109
IFWM3416	G	Y	S	F	T	S	Y	W	109

TABLE 25-continued

	HCDR1								
mAbs	Sequence								SEQ ID NO:
IFWM3310	G	Y	S	F	T	S	Y	W	109
IFWM3400	G	Y	S	F	T	S	Y	W	109
IFWM3321	G	Y	S	F	T	S	Y	W	109
IFWM3522	G	Y	S	F	T	S	Y	W	109
IFWM3524	G	Y	S	F	T	S	Y	W	109
IFWM3320	G	Y	S	F	T	S	Y	W	109
IFWM3304	G	Y	S	F	T	S	Y	W	109
IFWM3520	G	Y	S	F	T	S	Y	W	109
IFWM3399	G	Y	S	F	T	S	Y	W	109
IFWM3314	G	Y	S	F	T	S	Y	W	109
IFWM3331	G	Y	S	F	T	S	Y	W	109
IFWM3405	G	Y	S	F	T	S	Y	W	109
IFWM3442	G	Y	S	F	T	S	Y	W	109
IFWM3525	G	Y	S	F	T	S	Y	W	109
IFWM3423	G	Y	S	F	T	S	Y	W	109
IFWM3444	G	Y	S	F	T	S	Y	W	109
IFWM3421	G	Y	S	F	T	S	Y	W	109

TABLE 26

	HCDR2								
mAbs	Sequence								SEQ ID NO:
IFWM3308	I	D	P	S	D	S	D	T	113
IFWM3307	I	D	P	S	D	S	D	T	113
IFWM3410	I	D	P	S	D	S	D	T	113
IFWM3322	I	D	P	S	D	S	D	T	113
IFWM3385	I	D	P	S	D	S	D	T	113
IFWM3416	I	D	P	S	D	S	D	T	113
IFWM3310	I	D	P	S	D	S	D	T	113
IFWM3400	I	D	P	S	D	S	D	T	113
IFWM3321	I	D	P	S	D	S	D	T	113
IFWM3522	I	D	P	S	D	S	D	T	113
IFWM3524	I	D	P	S	D	S	D	T	113
IFWM3320	I	D	P	S	D	S	D	T	113
IFWM3304	I	D	P	S	D	S	D	T	113
IFWM3520	I	D	P	S	D	S	D	T	113
IFWM3399	I	D	P	S	D	S	D	T	113
IFWM3314	I	D	P	S	D	S	D	T	113
IFWM3331	I	D	P	S	D	S	D	T	113
IFWM3405	I	D	P	S	D	S	D	T	113
IFWM3442	I	A	P	S	D	S	D	T	111
IFWM3525	I	D	P	S	D	S	D	T	113
IFWM3423	I	D	P	S	D	S	D	T	113
IFWM3444	I	D	A	S	D	S	D	T	112
IFWM3421	I	D	P	S	D	S	D	T	113

TABLE 27

	HCDR3														
mAbs	Sequence														SEQ ID NO:
IFWM3308	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3307	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3410	A	R	H	P	G	L	A	W	A	P	D	F	D	Y	115
IFWM3322	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3385	A	R	H	P	G	L	A	W	A	P	D	F	D	Y	115
IFWM3416	A	R	H	P	G	L	A	W	A	P	D	F	D	Y	115
IFWM3310	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3400	A	R	H	P	G	L	A	W	A	P	D	F	D	Y	115
IFWM3321	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3522	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3524	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116

TABLE 27-continued

mAbs	HCDR3 Sequence														SEQ ID NO:
IFWM3320	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3304	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3520	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3399	A	R	H	P	G	L	A	W	A	P	D	F	D	Y	115
IFWM3314	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3331	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3405	A	R	H	P	G	L	A	W	A	P	D	F	D	Y	115
IFWM3442	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3525	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3423	A	R	H	P	G	L	A	W	A	P	D	F	D	Y	115
IFWM3444	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116
IFWM3421	A	R	H	P	G	L	N	W	A	P	D	F	D	Y	116

EXAMPLE 11

Anti-IFN-α/ω Antibodies Neutralize Leukocyte IFN

[0655] The ability of the antibodies to neutralize leukocyte IFN was assessed by the ability of the antibodies to inhibit IFN-induced IP-10 release from whole blood.

[0656] Select antibodies from the affinity-maturation campaign or after minimizing the PTM risk were characterized further for their ability to inhibit endogenous Type I IFN. All characterized antibodies were of IgG1/K type. Antibodies IFWM3522, IFWM3525, IFWM3399 and IFWM3423 were used in the assays.

IP-10 Release Assay:

[0657] 240 μl of whole blood (Biological Specialty Corporation) was added to individual wells in 96 well U-bottom plates containing 30 μl of antibody (anti IFN-α/ω or isotype control), with or without IFN or IFN-containing conditioned media diluted in cell culture media (RPMI1640 with 10% HI FBS and 1% penn strep). For stimulation, human leukocyte IFN (Sigma-Aldrich) was utilized at 250 U/ml (final volume) and SLE immune complex-treated conditioned media at 10 μl per well. IFN and antibody mixtures were preincubated at room temperature for 20-30 min prior to adding whole blood. Plates were incubated overnight for 20-22 hours at 37° C. The following day, plates were centrifuged at 400×g for 5 minutes at room temperature and plasma removed and frozen at −20° C. Duplicate samples from each treatment were analyzed using a CXCL10/IP-10 ELISA kit from Qiagen. Upon thawing, the collected plasma was diluted 2.5 fold using sample dilution buffer and used in the assay. Manufacturer's protocol was followed with slight modification in the dilution of standards as follows. Two fold serial dilutions of the antigen standard were made starting at a concentration of 4000pg/ml and ending at 31.25 pg/ml. Plates were read at an absorbance at 450 nm within 30 minutes of stopping the reaction. Analysis was performed using Softmax Pro.

Results

[0658] Select antibodies were characterized for their ability to neutralize endogenous IFN-I preparations in relevant cell types. IFN-I stimulation of whole blood induces IP-10 (CXCL10) release in vitro and in vivo (Arico, E. et al. Concomitant detection of IFNalpha signature and activated monocyte/dendritic cell precursors in the peripheral blood of IFNalpha-treated subjects at early times after repeated local cytokine treatments. *J Transl Med* 9, 67, doi:10.1186/1479-5876-9-67 (2011).; Mohty, A. M. et al. Induction of IP-10/CXCL10 secretion as an immunomodulatory effect of low-dose adjuvant interferon-alpha during treatment of melanoma. *Immunobiology* 215, 113-123, doi:10.1016/j.imbio.2009.03.008 (2010)). IP-10 is elevated in SLE, and has been shown in several studies to correlate with disease activity and clinical manifestations of disease (Bauer, J. W. et al. Interferon-regulated chemokines as biomarkers of systemic lupus erythematosus disease activity: a validation study. *Arthritis and rheumatism* 60, 3098-3107, doi:10.1002/art.24803 (2009).; Kong, K. O. et al. Enhanced expression of interferon-inducible protein-10 correlates with disease activity and clinical manifestations in systemic lupus erythematosus. *Clinical and experimental immunology* 156, 134-140, doi:10.1111/j.1365-2249.2009.03880.x (2009).; Rose, T. et al. IFNalpha and its response proteins, IP-10 and SIGLEC-1, are biomarkers of disease activity in systemic lupus erythematosus. *Annals of the rheumatic diseases* 72, 1639-1645, doi: 10.1136/annrheumdis-2012-201586 (2013).

[0659] The ability of anti IFN-α/ω mAbs to inhibit IP-10 release in whole blood induced by leukocyte IFN was examined in vitro. IFN-I is rapidly produced in response to infectious agents, such as viruses, to help control infection. Human leukocyte IFN is a natural mixture of IFNs produced by leukocytes after viral infection and is largely composed of INF-α subtypes and IFN-ω. IFN-ω is believed to constitute approximately 15% of the total IFN-I activity in these preparations. Importantly, infections are believed to potentially contribute to both induction and exacerbation of SLE. In this study, human leukocyte IFN was added to whole blood samples from 2 healthy human donors in the presence of inhibitors or controls and plasma was assessed for IP-10 release 24 h post IFN exposure. Anti IFN-α/ω mAbs: IFWM3522 and IFWM3525 (FIG. **11**A), and IFWM3399 (FIG. **11**B) all dose-dependently neutralized leukocyte IFN-induced IP-10 release in both donors tested.

EXAMPLE 12

Anti-IFN-α/ω Antibodies Neutralize SLE Immune Complexes

[0660] A hallmark of SLE is the presence of autoantibodies such as anti-double-stranded DNA (anti-dsDNA) that typi-

cally precede the development of clinically defined disease. Autoantibodies bound to nucleic acid ligands are thought to be endogenous inducers of type I IFN in SLE patients. The preponderance of autoantibodies in conjunction with impaired clearance of autoantigens leads to a feedback cycle of IFN production where Fc receptor-dependent internalization of immune complexes into plasmacytoid dendritic cells (pDC) leads to increased amounts of circulating IFN and establishment of the IFN gene signature.

[0661] We further tested the ability of the anti-IFN-α/ω antibodies to neutralize more disease relevant endogenous IFN preparations.

[0662] Immune complexes were prepared essentially as described in Example 1. These SLE patient-derived immune complexes were then added to healthy donor PBMCs and IFN-containing conditioned media collected from cell cultures (IC92 and IC163). Next, the conditioned media was added to healthy donor whole blood from 4 healthy donors in the presence of inhibitors or control to determine the impact of IFN-α/ω neutralization on IFN-induced IP-10 release. IFWM3522, IFWM3525, and IFWM3399 all dose-dependently neutralized IP-10 release using both SLE immune complex-induced IFN preps in all whole blood donors tested. FIG. **12**A shows neutralization of SLE immune complex-induced IFN-stimulated IP-10 release in human whole blood by antibodies IFWM3522 and IFWM2525 from one donor (SLE donor 92). FIG. **12**B shows the results for antibody IFWM3399 and isotype control.

EXAMPLE 13

Anti-IFN-α/ω Antibodies Neutralize SLE Plasma

[0663] Anti IFN-α/ω mAbs demonstrated potent dose-dependent neutralization of endogenous IFN-I preparations produced from human primary cells after exposure to both sterile (immune complex; Example 12) and microbial ligands (leukocyte IFN; Example 11). Potency of the IFN-α/ω mAbs to neutralize physiological Type I IFN was further assessed by the ability of the antibodies to neutralize IFN-I activity from SLE patient sera and plasma. This approach thus assesses ability of the antibodies to neutralize the actual circulating IFN-I milieu from the patient which may contain an IFN spectrum that may be difficult to recapitulate in vitro.

ISRE Assay using SLE Serum:

[0664] HEK Blue (a/β) cells (InvivoGen) were plated at 50,000 cells per well in a total volume of 200 μl DMEM+10% FBS and incubated overnight at 37° C. The next day, pooled plasma (3 donors) or serum (13 donors) pre-selected on the basis of achieving an OD of greater than or equal to 1.0 after a 30 minute incubation in this assay was thawed and mixed at a 1:1 (v/v) ratio with DMEM+10% FBS. Supernatants were removed from the previously plated Hek Blue cells and replaced with 100 μl of the SLE plasma or serum/media mixture and allowed to incubate overnight at 37° C. The next day, 40 μl conditioned media was removed and added to 160 μl Quanti-Blue substrate (InvivoGen) in a new plate and allowed to incubate for 30 minutes. Plates were read using a spectrophotometer at 650 nanometer wavelength and IC_{50} values were calculated using GraphPad Prism.

Results

[0665] SLE serum from a Chinese cohort of patients (SLE Cohort 1) and SLE plasma from a primarily African American cohort (SLE Cohort 2) was prescreened for IFN-I activity using the ISRE assay. SLE donor serum or plasma samples having an OD of ~1.0 or greater were determined to have a sufficient window of IFN-I activity such that inhibition with antagonist antibodies could be easily measured. These donor samples were then pooled to create a serum or plasma stock to generate enough sample volume to enable repeat experiments and antibody titrations. SLE patient samples from diverse racial/ethnic cohorts were utilized to better capture the potential diversity in qualitative and quantitative IFN-I responses in SLE patients. African American and Asian donors are thought to have higher IFN-I activity than Caucasian donors. The anti-IFN-α/ω mAbs tested dose-dependently neutralized IFN-I activity in pooled SLE patient serum and plasma samples. IC_{50} values from two independent experiments are shown using pooled samples from both SLE cohorts in Table 28.

TABLE 28

	Mean IC_{50} (ng/ml) +/− SD	
mAb	SLE Cohort 1 (serum)	SLE Cohort 2 (plasma)
IFWM3525	5.166 +/− 0.1612	4.255 +/− 0.8422
IFWM3522	10.47 +/− 0.3818	6.059 +/− 0.3613
IFWM3399	8.352 +/− 1.102	4.340 +/− 0.1223

EXAMPLE 14

Anti-IFN-α/ω Antibodies Neutralize IFN Gene Signature

[0666] Type I IFN induces a spectrum of genes that are also overexpressed in some SLE patients as compared to healthy controls. Plasma samples from SLE patients exhibiting this IFN gene signature are capable of inducing overexpression of a similar set of genes when added to healthy donor PBMCs or cell lines, and this activity is predominately neutralized by antibodies targeting INF-α (Hua et al., *Arthritis and rheumatism* 54, 1906-1916, doi:10.1002/art.21890 (2006)).

[0667] An assay was developed to determine the effect of the antibodies on normalizing the IFN-I signature present in the SLE patient heparinized whole blood. IFN-I inducible gene MX1 (myxovirus resistance 1) expression was used as a marker for IFN-I activity.

Materials

[0668] 2-4 h after collection of SLE or healthy blood into sodium heparin tubes, 240 μl was plated into 96 well U-bottom plates containing anti- IFN-α/ω antibodies or human IgG1 isotype control. Antibodies diluted in PBS were added at 30 μl per well to 240 μl of blood. After 24 h incubation at 37° C., 745 μl of PAXgene stabilization reagent (QIAGEN) was added to a 96 deep well plate and blood samples were transferred and mixed thoroughly by pipetting. Plates were sealed and frozen at -80° C. until further processing. After thawing, samples were transferred to 2 ml Safe-Lock tubes (Eppendorf) and spun at 5000×g for 10 minutes. Supernatants were aspirated and sample pellets resuspended in 432 μl of DNase/RNase free water by vortexing. Samples were further centrifuged at 5000×g and pellets resuspended in 350 μl BR1 buffer. 300 μl of BR2 buffer was next added followed by 40 μl of proteinase K and samples incubated at 55° C. and shaken at 800rpm for 10 minutes. The manufacturer's protocol was followed for remainder of purification (QIAGEN, cat#762164). 120 ng of total RNA from each sample was

converted to cDNA using iScript cDNA Synthesis kit (BIO-RAD) and primer/probe pairs for human MX1 and beta actin (ACTB) (cat# Hs00895608_ml and Hs01060665_gl, respectively) were utilized for qPCR. Data was collected on a Viia7 Real Time PCR system and analyzed us GraphPad Prism representing the change in expression of MX1 relative to the ACTB (dCT).

Results

[0669] The ability of the IFN-α/ω antibodies to decrease the IFN-I signature in patient blood was assessed using MX1 gene expression as a marker for IFN-I activity.

[0670] MX1 gene expression was increased approximately 7 fold in the blood of a SLE patient when compared to a healthy control. The tested anti-IFN-α/ω antibodies dose-dependently reduced MX1 expression in the blood of SLE patients after 24 hour incubation, and at highest antibody concentration the MX1 expression was normalized close to the levels observed in healthy control. FIG. **13** shows the effect of the antibody treatment on MX1 expression in one SLE donor normalized to beta actin expression and is representative of multiple donors having elevated baseline MX1 expression when compared to healthy controls.

EXAMPLE 15

Anti-IFN-α/ω Antibodies Neutralize Cyno Type I IFNs

[0671] The ability of the select anti-IFN-α/ω antibodies to neutralize various cyno Type I IFNs was assessed using the ISRE reporter gene assay.

[0672] Cynomolgus IFN-α2 (PBL Assay Sciences), IFN-α4 (Sino Biological), IFN-α8 (Sino Biological), and IFN-α13 (Sino Biological) were used in the assays. IC_{50} values were determined using previously determined EC_{75} values for each IFN. (0.078 ng/ml for IFN-α2, 2.68 ng/ml for IFN-α4, 0.66 ng/ml for IFN-α8 and 18.4 for IFN-α13). The IC_{50} of select anti-IFN-α/ω mAbs is shown in Table 29). The data in table 20 is an average of two independent experiments. IFN-α/ω mAbs IFWM3525 and IFWM3522 exhibited similar cross-neutralization properties between the human and orthologous cynomolgus antigens available to test. The lack of neutralization of cynomolgus IFN-α13 was expected, as this molecule, like human IFN-αD, has a serine at position 27 (S27).

TABLE 29

	Mean IC_{50} (ng/ml) +/− SD				
mAb	Cyno IFN-α13	Cyno IFN-α4	Cyno IFN-α2	Cyno IFN-α8	Cyno IFN-ω
IFWM3525	921.5 +/− 294.9	6.769 +/− 0.1923	3.346 +/− 0.1747	0.5668 +/− 0.07085	0.9568 +/− 0.1276
IFWM3522	8063 +/− 2562	7.348 +/− 0.7616	9.887 +/− 2.918	0.5497 +/− 0.03734	2.028 +/− 0.3691

EXAMPLE 16

Crystal Structure of IFWM3421 in Complex with IFN-ω T80E

[0673] Crystallization, X-ray data collection and structure determination was done essentially as described in Example 6, except for following changes:

[0674] The complex was prepared by mixing IFN-ω:Fab at 1.05:1.00 ratio (excess IFN-ω), incubated at 4° C. overnight, and then concentrated without purification to 8.37 mg/mL in 20 mM Tris pH 7.4, 50 mM NaCl. Crystals for X-ray data collection were obtained from HEPES pH 7.5, 0.2 M Li2SO4, 18% PEG 3350 with MMS seeding.

[0675] For X-ray data collection for the IFNω/Fab3186 complex, a crystal was soaked in synthetic mother liquor (0.1 M HEPES, pH 7.5, 20% PEG 3350, 0.2 M LiSO4 with 20% glycerol) and flash frozen in liquid nitrogen. X-ray data were collected at APS (Argonne National Lab). ELN ATeplyak-2013-0014. The diffraction data were processed with XDS. The structure refinement statistics are given in Table 30.

TABLE 30

	IFNω/FabM3421
Crystal data	
Space group	C2
Unit cell dimensions	
a, b, c (Å)	77.48, 69.89, 127.38
α, β, γ (°)	90, 102.39, 90
Asymmetric unit content	1 complex
X-ray data	
Resolution (Å)	50.00-1.90 (1.94-1.90)
Number of measured reflections	160,439 (10,287)
Number of unique reflections	49,423 (3,356)
Completeness (%)	98.3 (91.1)
R_{merge}	0.095 (0.643)
<I/σ>	9.8 (2.5)
B-factor (Wilson plot) (Å^2)	26.6
Refinement	
Resolution (Å)	44.36-1.90 (1.94-1.90)
Number of refls used in refinement	49,411 (2,292)
Number of all atoms	4,249
Number of water molecules	442
Rcryst (%)	19.0 (42.1)
Rfree (%)	22.8 (39.8)
RMSD bond lengths (Å)	0.008
RMSD bond angles (°)	1.12
RMSD B-factor main-chain (Å^2)	4.9
Mean B-factor (Å^2)	34.1
Protein	33.6
Solvent	38.3
MolProbity [25]	
Clash score	3.2
Rotamer outliers (%)	2.5
Ramachandran favored (%)	98.2
Ramachandran outliers (%)	0.0
Cβ deviation >0.25 Å	0

*Values for high-resolution shell are in parentheses

[0676] The crystal structure of IFNω/Fab3421 was determined to 1.9 A (Table 30). The IFN-ω model contained resi-

dues of 23-39 and 118-153. The majority of IFN-ω molecule did not have any electron density and there was no room for them in the crystal, suggesting that cleavage of IFN-ω also happened.

[0677] The overall structure of the IFN-ω/Fab3421 complex was very similar to IFNω/FabM371. The backbone structures of the individual components (VH, VL and IFNω) are all nearly identical (Ca rmsd 0.17, 0.23 and 0.36 Å, respectively).

[0678] There were, however, a number of significant structural differences. First, when the two structures were superimposed on the VL, the VH was rotated by 4 degrees and the antigen rotated by 11 degrees, leading to a large shift of the IFN-ω molecule with respect to VL. Second, H bonding and water structures (WC2 in particular) were different between the two structures (FIG. **14**A and 14B). R33 of IFN-ω makes 6 H bonds including a salt-bridge with D107 of HCDR3 in the parent M371 complex (FIG. **14**A). In the matured form, the side chain electron density for both R33 of IFN-ω and D107 of VH is less well defined (not shown) and they appear to be farther apart, thus reducing the number and strength of the charge-charge interactions (FIG. **14**B). A water molecule that involves H99 of VH in M371 is now absent (FIGS. **14**A, **14**B). Third, F108 of HCDR3 is not involved in antigen binding, but is part of the VL/VH interface. It adopts two alternative conformations in the parent structure (FIG. **14**C). The relative rotation of the VL/VH domains along with the L96I mutation in VL reduced it to a single rotamer. Thus it appears that part of the maturation mutations led to better pairing of the Fv. Fourth, two positions were mutated to F (A50F and Y32F) during maturation. Y32 forms two H bonds with the backbone of IFN-ω. But these were also lost as a result of mutation to F (FIG. **14**D). The A5OF mutation does not generate any new contact with the antigen. Rather its phenyl ring stacks with the VH W104, which in turn packs with the antigen (FIG. **14**D). In the LCDR3, two additional hydrophobic mutations (T94L and L96I) appear to form better hydrophobic pocket for L30 and F27 of the antigen. Two additional negative charge mutations (S39D and S93D) do not form any interactions, except with solvent. Overall, affinity improvement is the result of the maturation process that reduces polar interactions but favors/strengthens hydrophobic packing with the antigen as well as better VL/VH pairing.

[0679] The epitope and paratope residues. FIG. **15** shows the 2D interaction mAb between IFN-ω and IFWM3421. The epitope residues are identical to those in the M371 structure. The paratope residues are also almost identical (FIG. **15**). However, as described above, the maturation process resulted in a number of structural and interaction differences, which likely account for the improvement in binding affinity.

EXAMPLE 17

Crystal Structure of IFWM3525 1 in Complex with IFN-ω T80E

[0680] Crystallization, X-ray data collection and structure determination was done essentially as described in Example 6.

[0681] The complex was prepared by mixing of IFN-ω with Fab of IFWM3525 in molar ratio of 1.05:1.0 (excess IFN-ω, 1.92:1.12 mg), incubated at 4° C. overnight, and purified on Superdex 200 column equilibrated with 20 mm HEPES pH 7.5, 0.25 M NaCl, 10% glycerol, then concentrated to 9.79 mg/ml. Crystals suitable for X-diffraction were obtained from 18% PEG 3K, 0.2 M sodium citrate by MMS seeding with seeds from IFN-ω/Fab3186 crystals.

[0682] For X-ray data collection, one crystal of IFN-ω/IFWM3525 complex was soaked for a few seconds in a synthetic mother liquor (20% PEG 3350, 0.2 M sodium citrate, 25% glycerol), and flash frozen in the liquid nitrogen. X-ray data were collected at APS (Argonne National Lab). The diffraction data were processed with XDS[10].

[0683] The structure of the IFN-ω/IFWM3525 complex was solved by molecular replacement (MR) with Phaser. The search models for MR were the crystal structure of IFN-ω/FabM371. The structure was then refined with PHENIX and model adjustments were carried out using COOT. All other crystallographic calculations were performed with the CCP4 suite of programs. All molecular graphics were generated with PyMol. The structure refinement statistics are given in Table 31.

TABLE 31

	IFNω/Fab IFWM3525
Crystal data	
Space group	C2
Unit cell dimensions	
a, b, c (Å)	169.53, 132.78, 144.19
α, β, γ (°)	90, 120.43, 90
Asymmetric unit content	4 complex
X-ray data	
Resolution (Å)	50-3.14 (3.22-3.14)*
Number of measured reflections	161,700 (9,097)
Number of unique reflections	47,615 (3,033)
Completeness (%)	98.30 (85.1)
R_{merge}	0.106 (0.877)
$\langle I/\sigma \rangle$	10.7 (1.6)
B-factor (Wilson plot) (Å^2)	79.9
Refinement	
Resolution (Å)	47.9-3.14 (3.20-3.14)
Number of refls used in refinement	47,403 (2,685)
Number of all atoms	14,880
Number of solvent molecules	0
Rcryst (%)	24.4 (37.1)
Rfree (%)	28.4 (42.0)
RMSD bond lengths (Å)	0.002
RMSD bond angles (°)	0.60
RMSD B-factor main-chain (Å^2)	5.2
Mean B-factor (Å^2)	88.9
Protein	88.9
Solvent	N/A
MolProbity [25]	
Clash score	3.2
Rotamer outliers (%)	0.4
Ramachandran favored (%)	96.1
Ramachandran outliers (%)	0.3
Cβ deviation (>0.25 Å)	0

*Values for high-resolution shell are in parentheses

[0684] The overall structure of the IFN-ω/IFWM35258 complex was very similar to IFN-ω/FabM371. The molecular models for the IFN-ω molecules includes residues 23-39 and 119-153, corresponding to helical segment AB and helices D and E. The helices A, B and C and the connecting loops are disordered. These missing parts of the IFN-ω are likely due to limited proteolysis as found for the M371 and M3421 complex structures. The Fab molecular model contains residues from 1 to 213 for the light chain and from 1 to 222 for the heavy chain. The C-terminal 6×His tag, inter-chain disulfide

bond and residues of 137-141 of the heavy chain are disordered. No solvent water molecules were included due to low diffraction resolution.

[0685] FIG. **16** shows a 2-dimensional interaction map between IFN-ω and Fab of IFWM3525. Epitope residues F27, L30, and R33 of the AB helix account for the majority of the Ab/Ag interactions. Thus, this region of IFN-ω appears to constitute the main part of the epitope. Compared with the parental M371, the epitope contains two more residues from the helix E of IFN-ω which form interactions with HCDR3 of IFWM3525.

[0686] IFWM3525 has broad binding specificity for IFNω and most of IFNα subtypes. It does not bind IFNβ and IFNα-D/1. The sequence alignment of IFNs (FIG. **9**) indicates that IFWM3525 epitope residues are largely conserved among the IFN-ω and INF-α subtypes. In addition, structural comparison of the epitope residues in INF-α (pdb code 2RH2, which was re-built and refined using deposited data as only Cα trace was available in PDB) and IFN-ω indicate the epitope residues have very similar backbone and side chain structures. Thus, the sequence and structure conservations (or epitope conservation) likely are responsible for the broad binding of IFNα/ω by IFWM3525.

Sequence Listing

[0687]

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
1	PRT	*Homo sapiens*	human IFNw	CDLPQNHGLLSRNTLVLLHQMRRISPFLCLK DRRDFRFPQEMVKGSQLQKAHVMSVLHEMLQ QIFSLFHTERSSAAWNMTLLDQLHTGLHQQL QHLETCLLQVVGEGESAGAISSPALTLRRYF QGIRVYLKEKKYSDCAWEVVRMEIMKSLFLS TNMQERLRSKDRDLGSS
2	PRT	*Homo sapiens*	hu IFNw T80E	CDLPQNHGLLSRNTLVLLHQMRRISPFLCLK DRRDFRFPQEMVKGSQLQKAHVMSVLHEMLQ QIFSLFHTERSSAAWNMELLDQLHTGLHQQL QHLETCLLQVVGEGESAGAISSPALTLRRYF QGIRVYLKEKKYSDCAWEVVRMEIMKSLFLS TNMQERLRSKDRDLGSS
3	PRT	Chimp	chimp IFNomega	CDLPQNHGLLSRNTLVLLHQMRRISPFLCLK DRRDFRFPQEMVKGSQLQKAQVMSVLHEMLQ QIFSLFHTERSSAAWNMTLLDQLHTGLHQQL QHLETCLLQVMGEGESAGAISSPALTLRRYF QGIRVYLKEKKYSDCAWEVVRMEIMKSLFLS TNMQERLRSKDRDLGSSRNDSH
4	PRT	Cyno	cyno IFNomega	CDLPQNHGLLSRNTLVLLHQMRRISPFLCLK DRRDFRFPQEMVEGSQLQKAQVMSVLHEMLQ QIFSLFHTEHSSAAWNTTLLDHLHTGLHRQL EHLETCLVQVMREGESAGAIRSPALTLRRYF QGIRVYLKEKKYSDCAWVVVRMEIMKSLFLS TNMQERLKSKDGDLGSS
5	PRT	*Homo sapiens*	alpha A	CDLPQTHSLGSRRTLMLLAQMRKISLFSCLK DRHDFGFPQEEFGNQFQKAETIPVLHEMIQQ IFNLFSTKDSSAAWDETLLDKFYTELYQQLN DLEACVIQGVGVTETPLMKEDSILAVRKYFQ RITLYLKEKKYSPCAWEVVRAEIMRSFSLST NLQESLRSKE
6	PRT	*Homo sapiens*	IFN alpha B2	CDLPQTHSLGNRRALILLAQMRRISPFSCLK DRHDFEFPQEEFDDKQFQKAQAISVLHEMIQ QTFNLFSTKDSSAALDETLLDEFYIELDQQL NDLESCVMQEVGVIESPLMYEDSILAVRKYF QRITLYLTEKKYSSCAWEVVRAEIMRSFSLS INLQKRLKSKE
7	PRT	*Homo sapiens*	alpha C	CDLPQTHSLGNRRALILLGQMGRISPFSCLK DRHDFRIPQEEFDGNQFQKAQAISVLHEMIQ QTFNLFSTEDSSAAWEQSLLEKFSTELYQQL NDLEACVIQEVGVEETPLMNEDSILAVRKYF QRITLYLIERKYSPCAWEVVRAEIMRSLSFS TNLQKRLRRKD
8	PRT	*Homo sapiens*	alpha D	CDLPETHSLDNRRTLMLLAQMSRISPSSCLM DRHDFGFPQEEFDGNQFQKAPAISVLHELIQ QIFNLFTTKDSSAAWDEDLLDKFCTELYQQL NDLEACVMQEERVGETPLMNVDSILAVKKYF RRITLYLTEKKYSPCAWEVVRAEIMRSLSLS TNLQERLRRKE

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
9	PRT	*Homo sapiens*	alpha F	CDLPQTHSLGNRRALILLAQMGRISPFSCLK DRHDFGFPQEEFDGNQFQKAQAISVLHEMIQ QTFNLFSTKDSSATWEQSLLEKFSTELNQQL NDMEACVIQEVGVEETPLMNVDSILAVKKYF QRITLYLTEKKYSPCAWEVVRAEIMRSFSLS KIFQERLRRKE
10	PRT	*Homo sapiens*	alpha G	CDLPQTHSLSNRRTLMIMAQMGRISPFSCLK DRHDFGFPQEEFDGNQFQKAQAISVLHEMIQ QTFNLFSTKDSSATWDETLLDKFYTELYQQL NDLEACMMQEVGVEDTPLMNVDSILTVRKYF QRITLYLTEKKYSPCAWEVVRAEIMRSFSLS ANLQERLRRKE
11	PRT	*Homo sapiens*	alpha H2	CNLSQTHSLNNRRTLMLMAQMRRISPFSCLK DRHDFEFPQEEFDGNQFQKAQAISVLHEMMQ QTFNLFSTKNSSAAWDETLLEKFYIELFQQM NDLEACVIQEVGVEETPLMNEDSILAVKKYF QRITLYLMEKKYSPCAWEVVRAEIMRSLSFS TNLQKRLRRKD
12	PRT	*Homo sapiens*	IFN-aI	CDLPQTHSLGNRRALILLAQMGRISPFSCLKD RPDFGLPQEEFDGNQFQKTQAISVLHEMIQQ TFNLFSTEDSSAAWEQSLLEKFSTELYQQLNN LEACVIQEVGMEETPLMNEDSILAVRKYFQRI TLYLTEKKYSPCAWEVVRAEIMRSLSFSTNLQ KILRRKD
13	PRT	*Homo sapiens*	alpha J1	CDLPQTHSLRNRRALILLAQMGRISPFSCLK DRHEFRFPEEEFDGHQFQKTQAISVLHEMIQ QTFNLFSTEDSSAAWEQSLLEKFSTELYQQL NDLEACVIQEVGVEETPLMNEDFILAVRKYF QRITLYLMEKKYSPCAWEVVRAEIMRSFSFS TNLKKGLRRKD
14	PRT	*Homo sapiens*	alpha K	CDLPQTHSLGHRRTMMLLAQMRRISLFSCLK DRHDFRFPQEEFDGNQFQKAEAISVLHEVIQ QTFNLFSTKDSSVAWDERLLDKLYTELYQQL NDLEACVMQEVWVGGTPLMNEDSILAVRKYF QRITLYLTEKKYSPCAWEVVRAEIMRSFSSS RNLQERLRRKE
15	PRT	*Homo sapiens*	alpha 4b	CDLPQTHSLGNRRALILLAQMGRISHFSCLK DRHDFGFPEEEFDGHQFQKTQAISVLHEMIQ QTFNLFSTEDSSAAWEQSLLEKFSTELYQQL NDLEACVIQEVGVEETPLMNVDSILAVRKYF QRITLYLTEKKYSPCAWEVVRAEIMRSLSFS TNLQKRLRRKD
16	PRT	*Homo sapiens*	alpha WA	CDLPQTHSLGNRRALILLAQMGRISHFSCLK DRYDFGFPQEVFDGNQFQKAQAISAFHEMIQ QTFNLFSTKDSSAAWDETLLDKFYIELFQQL NDLEACVTQEVGVEEIALMNEDSILAVRKYF QRITLYLMGKKYSPCAWEVVRAEIMRSFSFS TNLQKGLRRKD
17	PRT	*Homo sapiens*	IFN-a2	CDLPQTHSLGSRRTLMLLAQMRRISLFSCLKD RHDFGFPQEEFGNQFQKAETIPVLHEMIQQI FNLFSTKDSSAAWDETLLDKFYTELYQQLNDL EACVIQGVGVTETPLMKEDSILAVRKYFQRITL YLKEKKYSPCAWEVVRAEIMRSFSLSTNLQES LRSKE
18	PRT	*Homo sapiens*	IFN-a1	CDLPETHSLDNRRTLMLLAQMSRISPSSCLM DRHDFGFPQEEFDGNQFQKAPAISVLHELIQ QIFNLFTTKDSSAAWDEDLLDKFCTELYQQLN DLEACVMQEERVGETPLMNADSILAVKKYFR RITLYLTEKKYSPCAWEVVRAEIMRSLSLSTNL QERLRRKE

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
19	PRT	*Homo sapiens*	IFN-a4a	CDLPQTHSLGNRRALILLAQMGRISHFSCLKD RHDFGFPEEEFDGHQFQKAQAISVLHEMIQQ TFNLFSTEDSSAAWEQSLLEKFSTELYQQLND LEACVIQEVGVEETPLMNEDSILAVRKYFQRIT LYLTEKKYSPCAWEVVRAEIMRSLSFSTNLQK RLRRKD
20	PRT	*Homo sapiens*	IFN-b	MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYC LKDRMNFDIPEEIKQLQQFQKEDAALTIYEML QNIFAIFRQDSSSTGWNETIVENLLANVYHQI NHLKTVLEEKLEKEDFTRGKLMSSLHLKRYYG RILHYLKAKEYSHCAWTIVRVEILRNFYFINRLT GYLRN
21	PRT	Artificial sequence	Signal peptide	MALTFYLLVALVVLSYKSFSSLG
22	PRT	Artificial sequence	Signal peptide	MARSFSLLMVVLVLSYKSICSLG
23	PRT	Artificial sequence	Signal peptide	MALPFALLMALVVLSCKSSCSLD
24	PRT	Artificial sequence	Signal peptide	MALSFSLLMAVLVLSYKSICSLG
25	PRT	Artificial sequence	Signal peptide	MALTFALLVALLVLSCKSSCSVG
26	PRT	*Homo sapiens*	IFNAR1	1 mmvvllgatt lvlvavapwv lsaaaggknl kspqkvevdi iddnfilrwn rsdesvgnvt 61 fsfdyqktgm dnwiklsgcq nitstkcnfs slklnvyeei klriraeken tsswyevdsf 121 tpfrkaqigp pevhleaedk aivihispgt kdsvmwaldg lsftyslviw knssgveeri 181 eniysrhkiy klspettycl kvkaalltsw kigvyspvhc ikttvenelp ppenievsvq 241 nqnyvlkwdy tyanmtfqvq wlhaflkrnp gnhlykwkqi pdcenvkttq cvfpqnvfqk 301 giyllrvqas dgnntsfwse eikfdteiqa fllppvfnir slsdsfhiyi gapkqsgntp 361 viqdypliye iifwentsna erkiiekktd vtvpnlkplt vycvkaraht mdeklnkssv 421 fsdavcektk pgntskiwli vgicialfal pfviyaakvf lrcinyvffp slkpssside 481 yfseqplknl llstseeqie kcfiienist iatveetnqt dedhkkyssq tsqdsgnysn 541 edesesktse elqqdfv
27	PRT	*Homo sapiens*	IFNAR2	1 mllsqnafif rslnlvlmvy islvfgisyd spdytdesct fkislrnfrs ilswelknhs 61 ivpthytlly timskpedlk vvkncanttr sfcdltdewr stheayvtvl egfsgnttlf 121 scshnfwlai dmsfeppefe ivgftnhinv mvkfpsivee elqfdlslvi eeqsegivkk 181 hkpeikgnms gnftyiidkl ipntnycvsv ylehsdeqav iksplkctll ppgqesesae 241 sakiggiitv flialvltst

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
				ivtlkwigyi clrnslpkvl rqglakgwna vaihrcshna 301 lqsetpelkq ssclsfpssw dykraslcps d
28	PRT	Artificial sequence	IFWH591	EVQLVQSGAEVKKPGESLKISCKGSGYSFTS YWIGWVRQMPGKGLEWMGIIDPSDSDTRYSP SFQGQVTISADKSISTAYLQWSSLKASDTAM YYCARHPGLNWAPDFDYWGQGTLVTVSS
29	PRT	Artificial sequence	PH9L4	DIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYS TPLTFGQGTKVEIK
30	PRT	Artificial sequence	IFWH624	EVQLVQSGAEVKKPGESLKISCKGSGYSFTS YWIGWVRQMPGKGLEWMGIIDPSDSDTAYSP SFQGQVTISADKSISTAYLQWSSLKASDTAM YYCARHPGLNWAPDFDYWGQGTLVTVSS
31	PRT	Artificial sequence	IFWH629	EVQLVQSGAEVKKPGESLKISCKGSGYSFTS YWIGWVRQMPGKGLEWMGIIDPSDSDTRYSP SFQGQVTISADKSISTAYLQWSSLKASDTAM YYCARHPGLAWAPDFDYWGQGTLVTVSS
32	PRT	Artificial sequence	IFWL983	DIQMTQSPSSLSASVGDRVTITCRASQSIDG SLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD FPLTFGQGTKVEIK
33	PRT	Artificial sequence	IFWL991	DIQMTQSPSSLSASVGDRVTITCRASQSINR FLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAID LPFTFGQGTKVEIK
34	PRT	Artificial sequence	IFWL992	DIQMTQSPSSLSASVGDRVTITCRASQSIGS FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYS IPITFGQGTKVEIK
35	PRT	Artificial sequence	IFWL997	DIQMTQSPSSLSASVGDRVTITCRASQSIGS ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD FPLTFGQGTKVEIK
36	PRT	Artificial sequence	IFWL998	DIQMTQSPSSLSASVGDRVTITCRASQSISK FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSNT LPFTFGQGTKVEIK
37	PRT	Artificial sequence	IFWL999	DIQMTQSPSSLSASVGDRVTITCRASQSIDE FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAHS FPLTFGQGTKVEIK
38	PRT	Artificial sequence	IFWL1000	DIQMTQSPSSLSASVGDRVTITCRASQSITN FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSLD FPLTFGQGTKVEIK
39	PRT	Artificial sequence	IFWL1001	DIQMTQSPSSLSASVGDRVTITCRASQSIGD FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQALD FPLTFGQGTKVEIK
40	PRT	Artificial sequence	IFWL1004	DIQMTQSPSSLSASVGDRVTITCRASQSIAE FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSID FPLTFGQGTKVEIK
41	PRT	Artificial sequence	IFWL1006	DIQMTQSPSSLSASVGDRVTITCRASQSIGG FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
				SGSGSGTDFTLTISSLQPEDFATYYCQQSYS LPITFGQGTKVEIK
42	PRT	Artificial sequence	IFWL1007	DIQMTQSPSSLSASVGDRVTITCRASQSIGK SLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD FPLTFGQGTKVEIK
43	PRT	Artificial sequence	IFWL1009	DIQMTQSPSSLSASVGDRVTITCRASQSIDD FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSHT LPLTFGQGTKVEIK
44	PRT	Artificial sequence	IFWL1010	DIQMTQSPSSLSASVGDRVTITCRASQSIDG ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSFD FPLTFGQGTKVEIK
45	PRT	Artificial sequence	IFWL1013	DIQMTQSPSSLSASVGDRVTITCRASQSINN FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSFN LPITFGQGTKVEIK
46	PRT	Artificial sequence	IFWL1014	DIQMTQSPSSLSASVGDRVTITCRASQSIDR ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSFD FPLTFGQGTKVEIK
47	PRT	Artificial sequence	IFWL1017	DIQMTQSPSSLSASVGDRVTITCRASQSITS SLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSFD LPLTFGQGTKVEIK
48	PRT	Artificial sequence	IFWL1022	DIQMTQSPSSLSASVGDRVTITCRASQSINE FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYS TPLTFGQGTKVEIK
49	PRT	Artificial sequence	IFWL1026	DIQMTQSPSSLSASVGDRVTITCRASQSISK FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD FPITFGQGTKVEIK
50	PRT	Artificial sequence	IFWL1038	DIQMTQSPSSLSASVGDRVTITCRASQSISE YLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSHS LPITFGQGTKVEIK
51	PRT	Artificial sequence	IFWL1041	DIQMTQSPSSLSASVGDRVTITCRASQSITG FLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSHD FPLTFGQGTKVEIK
52	PRT	Artificial sequence	IFWL1047	DIQMTQSPSSLSASVGDRVTITCRASQSING VLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSHD FPLTFGQGTKVEIK
53	PRT	Artificial sequence	IFWL1048	DIQMTQSPSSLSASVGDRVTITCRASQSIDG ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD FPLTFGQGTKVEIK
54	PRT	Artificial sequence	IFWL1051	DIQMTQSPSSLSASVGDRVTITCRASQSIAD FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSHS FPLTFGQGTKVEIK
55	PRT	Artificial sequence	IFWL1053	DIQMTQSPSSLSASVGDRVTITCRASQSITN HLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAHN FPLTFGQGTKVEIK

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
56	PRT	Artificial sequence	IFWL1060	DIQMTQSPSSLSASVGDRVTITCRASQSIRN SLNWYQQKPGKAPKLLIKWASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQLYD WPLTFGQGTKVEIK
57	PRT	Artificial sequence	IFWL1063	DIQMTQSPSSLSASVGDRVTITCRASQSIAN NNLNWYQQKPGKAPKLLIHWASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DTPFTFGQGTKVEIK
58	PRT	Artificial sequence	IFWL1064	DIQMTQSPSSLSASVGDRVTITCRASQSINN LNWYQQKPGKAPKLLIYWASSLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQGYDT PFTFGQGTKVEIK
59	PRT	Artificial sequence	IFWL1067	DIQMTQSPSSLSASVGDRVTITCRASQSIRN NNLNWYQQKPGKAPKLLIHWASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DTPFTFGQGTKVEIK
60	PRT	Artificial sequence	IFWL1071	DIQMTQSPSSLSASVGDRVTITCRASQSIRN NSLNWYQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQDY NWPLTFGQGTKVEIK
61	PRT	Artificial sequence	IFWL1073	DIQMTQSPSSLSASVGDRVTITCRASQSIDN SYLNWYQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGW DWPLTFGQGTKVEIK
62	PRT	Artificial sequence	IFWL1074	DIQMTQSPSSLSASVGDRVTITCRASQSIAN TNLNWYQQKPGKAPKLLIHWASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQWY DNPLTFGQGTKVEIK
63	PRT	Artificial sequence	IFWL1076	DIQMTQSPSSLSASVGDRVTITCRASQSIDN NNLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DWPLTFGQGTKVEIK
64	PRT	Artificial sequence	IFWL1082	DIQMTQSPSSLSASVGDRVTITCRASQSIRN NSLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQDY NWPLTFGQGTKVEIK
65	PRT	Artificial sequence	IFWL1084	DIQMTQSPSSLSASVGDRVTITCRASQSINY LNWYQQKPGKAPKLLIYGASSLQSGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQSHDW PITFGQGTKVEIK
66	PRT	Artificial sequence	IFWL1085	DIQMTQSPSSLSASVGDRVTITCRASQSIRN NYLNWYQQKPGKAPKLLIYAASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DTPLTFGQGTKVEIK
67	PRT	Artificial sequence	IFWL1087	DIQMTQSPSSLSASVGDRVTITCRASQSISN SNLNWYQQKPGKAPKLLIHWASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQWY DHPLTFGQGTKVEIK
68	PRT	Artificial sequence	IFWL1091	DIQMTQSPSSLSASVGDRVTITCRASQSIRN TNLNWYQQKPGKAPKLLIHWASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DTPFTFGQGTKVEIK
69	PRT	Artificial sequence	IFWL1093	DIQMTQSPSSLSASVGDRVTITCRASQSIAN NDLNWYQQKPGKAPKLLIHWASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQDY DWPLTFGQGTKVEIK

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
70	PRT	Artificial sequence	IFWL1049	DIQMTQSPSSLSASVGDRVTITCRASQSIAG FLNWYQQKPGKAPKLLIYYASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYS IPITFGQGTKVEIK
71	PRT	Artificial sequence	IFWL984	DIQMTQSPSSLSASVGDRVTITCRASQSIDG FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
72	DNA	Artificial sequence	cDNA of IFWL984	GATATTCAGATGACCCAGAGCCCGAGCAGC CTGAGCGCGAGCGTGGGCGATCGCGTGAC CATTACCTGCCGCGCGAGCCAGAGCATTGA TGGGTTCCTGAACTGGTATCAGCAGAAACC GGGCAAAGCGCCGAAACTGCTGATTTATTT CGCGAGCAGCCTGCAGAGCGGCGTGCCGA GCCGCTTTAGCGGCAGCGGCAGCGGCACC GATTTTACCCTGACCATTAGCAGCCTGCAGC CGGAAGATTTTGCGACCTATTATTGCCAGC AGTCCTACGACCTCCCGATTACATTTGGCCA GGGCACCAAAGTGGAAATTAAA
73	PRT	Artificial sequence	IFWL1136	DIQMTQSPSSLSASVGDRVTITCRASQSIEG ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD FPLTFGQGTKVEIK
74	PRT	Artificial sequence	IFWL1144	DIQMTQSPSSLSASVGDRVTITCRASQSIEG YLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD FPLTFGQGTKVEIK
75	PRT	Artificial sequence	IFWL1148	DIQMTQSPSSLSASVGDRVTITCRASQSISS ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD FPLTFGQGTKVEIK
76	PRT	Artificial sequence	LCDR1	QSIADF
77	PRT	Artificial sequence	LCDR1	QSIAEF
78	PRT	Artificial sequence	LCDR1	QSIANNN
79	PRT	Artificial sequence	LCDR1	QSIANTN
80	PRT	Artificial sequence	LCDR1	QSIDGA
81	PRT	Artificial sequence	LCDR1	QSIDGF
82	PRT	Artificial sequence	LCDR1	QSIDNSY
83	PRT	Artificial sequence	LCDR1	QSIDRA
84	PRT	Artificial sequence	LCDR1	QSIEGA
85	PRT	Artificial sequence	LCDR1	QSIGDF
86	PRT	Artificial sequence	LCDR1	QSIGKS
87	PRT	Artificial sequence	LCDR1	QSIGSA

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
88	PRT	Artificial sequence	LCDR1	QSINGV
89	PRT	Artificial sequence	LCDR1	QSIRNTN
90	PRT	Artificial sequence	LCDR1	QSISSA
91	PRT	Artificial sequence	LCDR1	QSISSF
92	DNA	Artificial sequence	cDNA of IFWL1164	GACATCCAAATGACGCAGTCTCCGAGCTCT CTGAGCGCATCCGTGGGCGATCGCGTAACT ATCACTTGTCGCGCCTCCCAGAGCATTGATA ACTCCTATCTCAATTGGTATCAACAAAAACC GGGTAAGGCACCGAAACTGCTGATTTACGG AGCGTCCTCTCTGCAGTCCGGTGTGCCGTC CCGTTTCTCCGGCAGCGGTTCTGGTACCGA TTTCACGCTGACCATCAGCTCTCTGCAACCG GAGGACTTTGCTACGTACTACTGCCAACAG GGCTACGATTTCCCTCTCACATTCGGCCAAG GTACCAAAGTGGAAATTAAA
93	PRT	Artificial sequence	LCDR2	FAS
94	PRT	Artificial sequence	LCDR2	GAS
95	PRT	Artificial sequence	LCDR2	WAS
96	PRT	Artificial sequence	LCDR3	QQALDFPLT
97	PRT	Artificial sequence	LCDR3	QQAYDFPLT
98	PRT	Artificial sequence	LCDR3	QQGWDWPLT
99	PRT	Artificial sequence	LCDR3	QQGYDFPLT
100	PRT	Artificial sequence	LCDR3	QQGYDTPFT
101	PRT	Artificial sequence	LCDR3	QQSFDFPLT
102	PRT	Artificial sequence	LCDR3	QQSHDFPLT
103	PRT	Artificial sequence	LCDR3	QQSHSFPLT
104	PRT	Artificial sequence	LCDR3	QQSIDFPLT
105	PRT	Artificial sequence	LCDR3	QQSYDFPLT
106	PRT	Artificial sequence	LCDR3	QQSYDLPIT
107	PRT	Artificial sequence	LCDR3	QQWYDNPLT
108	DNA	Artificial sequence	cDNA of IFWL1048	GATATTCAGATGACCCAGAGCCCGAGCAGC CTGAGCGCGAGCGTGGGCGATCGCGTGAC CATTACCTGCCGCGCGAGCCAGAGCATCGA

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
				TGGCGCCCTGAACTGGTATCAGCAGAAACC GGGCAAAGCGCCGAAACTGCTGATTTATTT CGCGAGCAGCCTGCAGAGCGGCGTGCCGA GCCGCTTTAGCGGCAGCGGCAGCGGCACC GATTTTACCCTGACCATTAGCAGCCTGCAGC CGGAAGATTTTGCGACCTATTATTGCCAGC AGGCCTACGACTTTCCGTTGACATTTGGCCA GGGCACCAAAGTGGAAATTAAA
109	PRT	Artificial	HCDR1	GYSFTSYW
110	DNA	Artificial sequence	cDNA of IFWH591	GAGGTGCAGCTGGTGCAGAGCGGCGCCGA GGTGAAGAAGCCCGGCGAGAGCCTGAAGA TCAGCTGCAAGGGCAGCGGCTACAGCTTCA CCAGCTACTGGATCGGCTGGGTGCGGCAG ATGCCCGGCAAGGGCCTGGAGTGGATGGG CATCATCGACCCCAGCGACAGCGACACCCG GTACAGCCCCAGCTTCCAGGGCCAGGTGAC CATCAGCGCCGACAAGAGCATCAGCACCGC CTACCTGCAGTGGAGCAGCCTGAAGGCCA GCGACACCGCCATGTACTACTGCGCCCGGC ACCCCGGCCTGAACTGGGCCCCCGACTTCG ACTACTGGGGCCAGGGCACCCTGGTGACC GTGAGCAGC
111	DNA	Artificial sequence	HCDR2	IAPSDSDT
112	DNA	Artificial sequence	HCDR2	IDASDSDT
113	DNA	Artificial sequence	HCDR2	IDPSDSDT
114	PRT	Artificial	HCDR2 consensus sequence mAbs neutralize at least 3 IFNalphas	$IX_{11}X_{12}SDSDT$; whrein X_{11} is D or A; and X_{12} is P or A.
115	PRT	Artificial	HCDR3	ARHPGLAWAPDFDY
116	PRT	Artificial	HCDR3	ARHPGLNWAPDFDY
117	DNA	Artificial sequence	cDNA of IFWH617	GAGGTGCAGCTGGTGCAGAGCGGCGCCGA GGTGAAGAAGCCCGGCGAGAGCCTGAAGA TCAGCTGCAAGGGCAGCGGCTACAGCTTCA CCAGCTACTGGATCGGCTGGGTGCGGCAG ATGCCCGGCAAGGGCCTGGAGTGGATGGG CATCATCGACGCCAGCGACAGCGACACCCG GTACAGCCCCAGCTTCCAGGGCCAGGTGAC CATCAGCGCCGACAAGAGCATCAGCACCGC CTACCTGCAGTGGAGCAGCCTGAAGGCCA GCGACACCGCCATGTACTACTGCGCCCGGC ACCCCGGCCTGAACTGGGCCCCCGACTTCG ACTACTGGGGCCAGGGCACCCTGGTGACC GTGAGCAGC
118	PRT	Artificial	LCDR1 consensus sequence mAbs neutralize at least 3 IFNalphas	$QSIX_1X_2X_3X_4$; wherein X_1 is G, D, A, R, E, S, or N; X_2 is D, G, N, S, R, E or K; X_3 is F, A, N, T, S or V; X_4 is Y, N or deleted.
119	PRT	Artificial	LCDR2 consensus sequence mAbs	X_5AS; wherein X_5 is F, W or G.

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
			neutralize at least 3 IFNalphas	
120	PRT	Artificial	LCDR3 consensus sequence mAbs neutralize at least 3 IFNalphas	QQX$_6$X$_7$X$_8$X$_9$PX$_{10}$T; wherein X$_6$ is A, G, S or W; X$_7$ is L, Y, H, W, F or I; X$_8$ is D or S; X$_9$ is F, T, L, N or W; and X$_{10}$ is L, F or I.
121	PRT	Artificial	HCDR3 consensus sequence mAbs neutralize at least 3 IFNalphas	ARHPGLX$_{13}$WAPDFDY; wherein X$_{13}$ is A or N.
122	DNA	Artificial sequence	cDNA of IFWH629	GAGGTGCAGCTGGTGCAGAGCGGCGCCGA GGTGAAGAAGCCCGGCGAGAGCCTGAAGA TCAGCTGCAAGGGCAGCGGCTACAGCTTCA CCAGCTACTGGATCGGCTGGGTGCGGCAG ATGCCCGGCAAGGGCCTGGAGTGGATGGG CATCATCGACCCCAGCGACAGCGACACCCG GTACAGCCCCAGCTTCCAGGGCCAGGTGAC CATCAGCGCCGACAAGAGCATCAGCACCGC CTACCTGCAGTGGAGCAGCCTGAAGGCCA GCGACACCGCCATGTACTACTGCGCCCGGC ACCCCGGCCTGGCCTGGGCCCCCGACTTCG ACTACTGGGGCCAGGGCACCCTGGTGACC GTGAGCAGC
123	PRT	Artificial	IFWL1112	DIQMTQSPSSLSASVGDRVTITCRASQSISG FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
124	PRT	Artificial	IFWL1113	DIQMTQSPSSLSASVGDRVTITCRASQSIEG FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
125	PRT	Artificial	IFWL1114	DIQMTQSPSSLSASVGDRVTITCRASQSIDG YLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
126	PRT	Artificial	IFWL1115	DIQMTQSPSSLSASVGDRVTITCRASQSIDG FLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
127	PRT	Artificial	IFWL1117	DIQMTQSPSSLSASVGDRVTITCRASQSIDG FLNWYQQKPGKAPKLLIYIASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
128	PRT	Artificial	IFWL1118	DIQMTQSPSSLSASVGDRVTITCRASQSIDG FLNWYQQKPGKAPKLLIYLASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
129	PRT	Artificial	IFWL1119	DIQMTQSPSSLSASVGDRVTITCRASQSIDG FLNWYQQKPGKAPKLLIYIASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
130	PRT	Artificial	IFWL1120	DIQMTQSPSSLSASVGDRVTITCRASQSIEG YLNWYQQKPGKAPKLLIYFASSLQSGVPSRF

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
				SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
131	PRT	Artificial	IFWL1121	DIQMTQSPSSLSASVGDRVTITCRASQSIEG FLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
132	PRT	Artificial	IFWL1122	DIQMTQSPSSLSASVGDRVTITCRASQSIEG FLNWYQQKPGKAPKLLIYIASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
133	PRT	Artificial	IFWL1123	DIQMTQSPSSLSASVGDRVTITCRASQSIEG FLNWYQQKPGKAPKLLIYLASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
134	PRT	Artificial	IFWL1124	DIQMTQSPSSLSASVGDRVTITCRASQSIEG FLNWYQQKPGKAPKLLIYYASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
135	PRT	Artificial	IFWL1125	DIQMTQSPSSLSASVGDRVTITCRASQSISS FLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
136	PRT	Artificial	IFWL1126	DIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
137	PRT	Artificial	IFWL1129	DIQMTQSPSSLSASVGDRVTITCRASQSIGD FLNWYQQKPGKAPKLLIYYASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
138	PRT	Artificial	IFWL1173	DIQMTQSPSSLSASVGDRVTITCRASQSIEG YLNWYQQKPGKAPKLLIYYASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
139	PRT	Artificial	IFWL1174	DIQMTQSPSSLSASVGDRVTITCRASQSIEG FLNWYQQKPGKAPKLLIYYASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
140	PRT	Artificial	IFWL1175	DIQMTQSPSSLSASVGDRVTITCRASQSISS FLNWYQQKPGKAPKLLIYYASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYD LPITFGQGTKVEIK
141	PRT	Artificial	IFWL1135	DIQMTQSPSSLSASVGDRVTITCRASQSISG ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD FPLTFGQGTKVEIK
142	PRT	Artificial	IFWL1137	DIQMTQSPSSLSASVGDRVTITCRASQSIDG YLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD FPLTFGQGTKVEIK
143	PRT	Artificial	IFWL1143	DIQMTQSPSSLSASVGDRVTITCRASQSIDG ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD LPLTFGQGTKVEIK
144	PRT	Artificial	IFWL1149	DIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD FPLTFGQGTKVEIK

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
145	PRT	Artificial	IFWL1152	DIQMTQSPSSLSASVGDRVTITCRASQSISS ALNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD LPLTFGQGTKVEIK
146	PRT	Artificial	IFWL1155	DIQMTQSPSSLSASVGDRVTITCRASQSISS YLNWYQQKPGKAPKLLIYFASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD LPLTFGQGTKVEIK
147	PRT	Artificial	IFWL1161	DIQMTQSPSSLSASVGDRVTITCRASQSIGD FLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQAYD LPLTFGQGTKVEIK
148	PRT	Artificial	IFWL1162	DIQMTQSPSSLSASVGDRVTITCRASQSIDN SYLNWYQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DWPLTFGQGTKVEIK
149	PRT	Artificial	IFWL1163	DIQMTQSPSSLSASVGDRVTITCRASQSIDN SYLNWYQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGW DFPLTFGQGTKVEIK
150	PRT	Artificial	IFWL1164	DIQMTQSPSSLSASVGDRVTITCRASQSIDN SYLNWYQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DFPLTFGQGTKVEIK
151	PRT	Artificial	IFWL1176	DIQMTQSPSSLSASVGDRVTITCRASQSIDQ SYLNWYQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DFPLTFGQGTKVEIK
152	PRT	Artificial	IFWL1177	DIQMTQSPSSLSASVGDRVTITCRASQSIDT SYLNWYQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DFPLTFGQGTKVEIK
153	PRT	Artificial	IFWL1178	DIQMTQSPSSLSASVGDRVTITCRASQSIDN TYLNWYQQKPGKAPKLLIYGASSLQSGVPSR FSGSGSGTDFTLTISSLQPEDFATYYCQQGY DFPLTFGQGTKVEIK
154	PRT	Artificial	LCDR3	QQSYDFPL
155	PRT	*Homo sapiens*	IGHV5-51	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY WIGWVRQMPGKGLEWMGIIYPGDSDTRYS PSFQGQVTISADKSISTAYLQWSSLKASDTAV YYCAR
156	PRT	*Homo sapiens*	IGKV1D-39	DIQMTQSPSSLSASVGDRVTITCRASQSISSYL NWYQQKPGKAPKLLIYAASSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQSYSTPW TFGQGTKVEIK
157	PRT	Artificial sequence	IFWH615	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY WIGWVRQMPGKGLEWMGIIAPSDSDTRYS PSFQGQVTISADKSISTAYLQWSSLKASDTAM YYCARHPGLNWAPDFDYWGQGTLVTVSS
158	PRT	Artificial sequence	IFWH617	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY WIGWVRQMPGKGLEWMGIIDASDSDTRYS PSFQGQVTISADKSISTAYLQWSSLKASDTAM YYCARHPGLNWAPDFDYWGQGTLVTVSS

-continued

SEQ ID NO:	Type	Species	Description	Amino acid sequence (or nucleotide sequence, as applicable)
159	PRT	Artificial	LCDR1 consensus sequence mAbs neutralize at least 6 IFNalphas	QSIX$_{14}$X$_{15}$X$_{16}$X$_{17}$; wherein X$_{14}$ is G, D, A, E, S, or N; X$_{15}$ is D, G, N, S or R; X$_{16}$ is F, A, N, S or V; and X$_{17}$ is Y, N or deleted.
160	PRT	Artificial	LCDR3 consensus sequence mAbs neutralize at least 6 IFNalphas	QQX$_{18}$X$_{19}$X$_{20}$X$_{21}$PX$_{22}$T; wherein X$_{18}$ is A, G or S; X$_{19}$ is Y, H, W or F; X$_{20}$ is D or S; X$_{21}$ is F, T, L or W; and X$_{22}$ is L, F or I.
161	PRT	Artificial	LCDR1 consensus sequence mAbs neutralize at least 10 IFNalphas	QSIX$_{23}$X$_{24}$X$_{25}$X$_{26}$; wherein X$_{23}$ is A or D; X$_{24}$ is N or G; X$_{25}$ is F, N or S; and X$_{26}$ is Y, N or deleted.
162	PRT	Artificial	LCDR3 consensus sequence mAbs neutralize at least 10 IFNalphas	QQX$_{27}$X$_{28}$X$_{29}$X$_{30}$PX$_{31}$T; wherein X$_{27}$ is G or S; X$_{28}$ is Y; X$_{29}$ is D; X$_{30}$ is F, T or L; and X$_{31}$ is L, F or I.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 162

<210> SEQ ID NO 1
<211> LENGTH: 172
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

```
Cys Asp Leu Pro Gln Asn His Gly Leu Leu Ser Arg Asn Thr Leu Val
1               5                   10                  15

Leu Leu His Gln Met Arg Arg Ile Ser Pro Phe Leu Cys Leu Lys Asp
            20                  25                  30

Arg Arg Asp Phe Arg Phe Pro Gln Glu Met Val Lys Gly Ser Gln Leu
        35                  40                  45

Gln Lys Ala His Val Met Ser Val Leu His Glu Met Leu Gln Gln Ile
    50                  55                  60

Phe Ser Leu Phe His Thr Glu Arg Ser Ser Ala Ala Trp Asn Met Thr
65                  70                  75                  80

Leu Leu Asp Gln Leu His Thr Gly Leu His Gln Gln Leu Gln His Leu
                85                  90                  95

Glu Thr Cys Leu Leu Gln Val Val Gly Glu Gly Glu Ser Ala Gly Ala
            100                 105                 110

Ile Ser Ser Pro Ala Leu Thr Leu Arg Arg Tyr Phe Gln Gly Ile Arg
        115                 120                 125

Val Tyr Leu Lys Glu Lys Lys Tyr Ser Asp Cys Ala Trp Glu Val Val
```

-continued

```
    130                 135                 140

Arg Met Glu Ile Met Lys Ser Leu Phe Leu Ser Thr Asn Met Gln Glu
145                 150                 155                 160

Arg Leu Arg Ser Lys Asp Arg Asp Leu Gly Ser Ser
                165                 170


<210> SEQ ID NO 2
<211> LENGTH: 172
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Cys Asp Leu Pro Gln Asn His Gly Leu Leu Ser Arg Asn Thr Leu Val
1               5                   10                  15

Leu Leu His Gln Met Arg Arg Ile Ser Pro Phe Leu Cys Leu Lys Asp
            20                  25                  30

Arg Arg Asp Phe Arg Phe Pro Gln Glu Met Val Lys Gly Ser Gln Leu
        35                  40                  45

Gln Lys Ala His Val Met Ser Val Leu His Glu Met Leu Gln Gln Ile
    50                  55                  60

Phe Ser Leu Phe His Thr Glu Arg Ser Ser Ala Ala Trp Asn Met Glu
65                  70                  75                  80

Leu Leu Asp Gln Leu His Thr Gly Leu His Gln Gln Leu Gln His Leu
                85                  90                  95

Glu Thr Cys Leu Leu Gln Val Val Gly Glu Gly Glu Ser Ala Gly Ala
            100                 105                 110

Ile Ser Ser Pro Ala Leu Thr Leu Arg Arg Tyr Phe Gln Gly Ile Arg
        115                 120                 125

Val Tyr Leu Lys Glu Lys Lys Tyr Ser Asp Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Met Glu Ile Met Lys Ser Leu Phe Leu Ser Thr Asn Met Gln Glu
145                 150                 155                 160

Arg Leu Arg Ser Lys Asp Arg Asp Leu Gly Ser Ser
                165                 170


<210> SEQ ID NO 3
<211> LENGTH: 177
<212> TYPE: PRT
<213> ORGANISM: Pan troglodytes

<400> SEQUENCE: 3

Cys Asp Leu Pro Gln Asn His Gly Leu Leu Ser Arg Asn Thr Leu Val
1               5                   10                  15

Leu Leu His Gln Met Arg Arg Ile Ser Pro Phe Leu Cys Leu Lys Asp
            20                  25                  30

Arg Arg Asp Phe Arg Phe Pro Gln Glu Met Val Lys Gly Ser Gln Leu
        35                  40                  45

Gln Lys Ala Gln Val Met Ser Val Leu His Glu Met Leu Gln Gln Ile
    50                  55                  60

Phe Ser Leu Phe His Thr Glu Arg Ser Ser Ala Ala Trp Asn Met Thr
65                  70                  75                  80

Leu Leu Asp Gln Leu His Thr Gly Leu His Gln Gln Leu Gln His Leu
                85                  90                  95

Glu Thr Cys Leu Leu Gln Val Met Gly Glu Gly Glu Ser Ala Gly Ala
```

-continued

```
            100                 105                 110

Ile Ser Ser Pro Ala Leu Thr Leu Arg Arg Tyr Phe Gln Gly Ile Arg
        115                 120                 125

Val Tyr Leu Lys Glu Lys Lys Tyr Ser Asp Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Met Glu Ile Met Lys Ser Leu Phe Leu Ser Thr Asn Met Gln Glu
145                 150                 155                 160

Arg Leu Arg Ser Lys Asp Arg Asp Leu Gly Ser Ser Arg Asn Asp Ser
                165                 170                 175

His


<210> SEQ ID NO 4
<211> LENGTH: 172
<212> TYPE: PRT
<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 4

Cys Asp Leu Pro Gln Asn His Gly Leu Leu Ser Arg Asn Thr Leu Val
1               5                   10                  15

Leu Leu His Gln Met Arg Arg Ile Ser Pro Phe Leu Cys Leu Lys Asp
            20                  25                  30

Arg Arg Asp Phe Arg Phe Pro Gln Glu Met Val Glu Gly Ser Gln Leu
        35                  40                  45

Gln Lys Ala Gln Val Met Ser Val Leu His Glu Met Leu Gln Gln Ile
    50                  55                  60

Phe Ser Leu Phe His Thr Glu His Ser Ser Ala Ala Trp Asn Thr Thr
65                  70                  75                  80

Leu Leu Asp His Leu His Thr Gly Leu His Arg Gln Leu Glu His Leu
                85                  90                  95

Glu Thr Cys Leu Val Gln Val Met Arg Glu Gly Glu Ser Ala Gly Ala
            100                 105                 110

Ile Arg Ser Pro Ala Leu Thr Leu Arg Arg Tyr Phe Gln Gly Ile Arg
        115                 120                 125

Val Tyr Leu Lys Glu Lys Lys Tyr Ser Asp Cys Ala Trp Val Val Val
    130                 135                 140

Arg Met Glu Ile Met Lys Ser Leu Phe Leu Ser Thr Asn Met Gln Glu
145                 150                 155                 160

Arg Leu Lys Ser Lys Asp Gly Asp Leu Gly Ser Ser
                165                 170


<210> SEQ ID NO 5
<211> LENGTH: 165
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Lys Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60
```

-continued

```
Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210> SEQ ID NO 6
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu Ile
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Glu Phe Pro Gln Glu Glu Phe Asp Asp Lys Gln Phe
        35                  40                  45

Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60

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

Leu Leu Asp Glu Phe Tyr Ile Glu Leu Asp Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ser Cys Val Met Gln Glu Val Gly Val Ile Glu Ser Pro Leu Met
            100                 105                 110

Tyr Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Ser Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Ile Asn Leu Gln Lys
145                 150                 155                 160

Arg Leu Lys Ser Lys Glu
                165


<210> SEQ ID NO 7
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu Ile
1               5                   10                  15

Leu Leu Gly Gln Met Gly Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
            20                  25                  30
```

-continued

```
Arg His Asp Phe Arg Ile Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Glu Asp Ser Ser Ala Ala Trp Glu Gln Ser
65                  70                  75                  80

Leu Leu Glu Lys Phe Ser Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
            100                 105                 110

Asn Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Ile Glu Arg Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Leu Ser Phe Ser Thr Asn Leu Gln Lys
145                 150                 155                 160

Arg Leu Arg Arg Lys Asp
                165


<210> SEQ ID NO 8
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Cys Asp Leu Pro Glu Thr His Ser Leu Asp Asn Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Ser Arg Ile Ser Pro Ser Ser Cys Leu Met Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Pro Ala Ile Ser Val Leu His Glu Leu Ile Gln Gln Ile
    50                  55                  60

Phe Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp
65                  70                  75                  80

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

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
            100                 105                 110

Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
145                 150                 155                 160

Arg Leu Arg Arg Lys Glu
                165


<210> SEQ ID NO 9
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9
```

-continued

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

Leu Leu Ala Gln Met Gly Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Thr Trp Glu Gln Ser
65                  70                  75                  80

Leu Leu Glu Lys Phe Ser Thr Glu Leu Asn Gln Gln Leu Asn Asp Met
                85                  90                  95

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
            100                 105                 110

Asn Val Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Lys Ile Phe Gln Glu
145                 150                 155                 160

Arg Leu Arg Arg Lys Glu
                165


<210> SEQ ID NO 10
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Cys Asp Leu Pro Gln Thr His Ser Leu Ser Asn Arg Arg Thr Leu Met
1               5                   10                  15

Ile Met Ala Gln Met Gly Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Thr Trp Asp Glu Thr
65                  70                  75                  80

Leu Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ala Cys Met Met Gln Glu Val Gly Val Glu Asp Thr Pro Leu Met
            100                 105                 110

Asn Val Asp Ser Ile Leu Thr Val Arg Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Ala Asn Leu Gln Glu
145                 150                 155                 160

Arg Leu Arg Arg Lys Glu
                165
```

-continued

<210> SEQ ID NO 11
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Cys Asn Leu Ser Gln Thr His Ser Leu Asn Asn Arg Arg Thr Leu Met
1 5 10 15

Leu Met Ala Gln Met Arg Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
20 25 30

Arg His Asp Phe Glu Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
35 40 45

Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Met Gln Gln Thr
50 55 60

Phe Asn Leu Phe Ser Thr Lys Asn Ser Ser Ala Ala Trp Asp Glu Thr
65 70 75 80

Leu Leu Glu Lys Phe Tyr Ile Glu Leu Phe Gln Gln Met Asn Asp Leu
85 90 95

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
100 105 110

Asn Glu Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Gln Arg Ile Thr
115 120 125

Leu Tyr Leu Met Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
130 135 140

Arg Ala Glu Ile Met Arg Ser Leu Ser Phe Ser Thr Asn Leu Gln Lys
145 150 155 160

Arg Leu Arg Arg Lys Asp
165

<210> SEQ ID NO 12
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu Ile
1 5 10 15

Leu Leu Ala Gln Met Gly Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
20 25 30

Arg Pro Asp Phe Gly Leu Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
35 40 45

Gln Lys Thr Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
50 55 60

Phe Asn Leu Phe Ser Thr Glu Asp Ser Ser Ala Ala Trp Glu Gln Ser
65 70 75 80

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

Glu Ala Cys Val Ile Gln Glu Val Gly Met Glu Glu Thr Pro Leu Met
100 105 110

Asn Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
115 120 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
130 135 140

Arg Ala Glu Ile Met Arg Ser Leu Ser Phe Ser Thr Asn Leu Gln Lys

-continued

```
145                 150                 155                 160

Ile Leu Arg Arg Lys Asp
                165


<210> SEQ ID NO 13
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

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

Leu Leu Ala Gln Met Gly Arg Ile Ser Pro Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Glu Phe Arg Phe Pro Glu Glu Glu Phe Asp Gly His Gln Phe
        35                  40                  45

Gln Lys Thr Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Glu Asp Ser Ser Ala Ala Trp Glu Gln Ser
65                  70                  75                  80

Leu Leu Glu Lys Phe Ser Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
            100                 105                 110

Asn Glu Asp Phe Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Met Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Phe Ser Phe Ser Thr Asn Leu Lys Lys
145                 150                 155                 160

Gly Leu Arg Arg Lys Asp
                165


<210> SEQ ID NO 14
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

Cys Asp Leu Pro Gln Thr His Ser Leu Gly His Arg Arg Thr Met Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Arg Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Glu Ala Ile Ser Val Leu His Glu Val Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Val Ala Trp Asp Glu Arg
65                  70                  75                  80

Leu Leu Asp Lys Leu Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ala Cys Val Met Gln Glu Val Trp Val Gly Gly Thr Pro Leu Met
            100                 105                 110

Asn Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
```

-continued

```
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Phe Ser Ser Ser Arg Asn Leu Gln Glu
145                 150                 155                 160

Arg Leu Arg Arg Lys Glu
                165


<210> SEQ ID NO 15
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu Ile
1               5                   10                  15

Leu Leu Ala Gln Met Gly Arg Ile Ser His Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Glu Glu Glu Phe Asp Gly His Gln Phe
        35                  40                  45

Gln Lys Thr Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Glu Asp Ser Ser Ala Ala Trp Glu Gln Ser
65                  70                  75                  80

Leu Leu Glu Lys Phe Ser Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
            100                 105                 110

Asn Val Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Leu Ser Phe Ser Thr Asn Leu Gln Lys
145                 150                 155                 160

Arg Leu Arg Arg Lys Asp
                165


<210> SEQ ID NO 16
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu Ile
1               5                   10                  15

Leu Leu Ala Gln Met Gly Arg Ile Ser His Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg Tyr Asp Phe Gly Phe Pro Gln Glu Val Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Gln Ala Ile Ser Ala Phe His Glu Met Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr
65                  70                  75                  80

Leu Leu Asp Lys Phe Tyr Ile Glu Leu Phe Gln Gln Leu Asn Asp Leu
```

-continued

```
                85                  90                  95

Glu Ala Cys Val Thr Gln Glu Val Gly Val Glu Glu Ile Ala Leu Met
            100                 105                 110

Asn Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Met Gly Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Phe Ser Phe Ser Thr Asn Leu Gln Lys
145                 150                 155                 160

Gly Leu Arg Arg Lys Asp
                165


<210> SEQ ID NO 17
<211> LENGTH: 165
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Ser Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Arg Arg Ile Ser Leu Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Gly Asn Gln Phe Gln
        35                  40                  45

Lys Ala Glu Thr Ile Pro Val Leu His Glu Met Ile Gln Gln Ile Phe
    50                  55                  60

Asn Leu Phe Ser Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Thr Leu
65                  70                  75                  80

Leu Asp Lys Phe Tyr Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu Glu
                85                  90                  95

Ala Cys Val Ile Gln Gly Val Gly Val Thr Glu Thr Pro Leu Met Lys
            100                 105                 110

Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr Leu
        115                 120                 125

Tyr Leu Lys Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val Arg
    130                 135                 140

Ala Glu Ile Met Arg Ser Phe Ser Leu Ser Thr Asn Leu Gln Glu Ser
145                 150                 155                 160

Leu Arg Ser Lys Glu
                165


<210> SEQ ID NO 18
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Cys Asp Leu Pro Glu Thr His Ser Leu Asp Asn Arg Arg Thr Leu Met
1               5                   10                  15

Leu Leu Ala Gln Met Ser Arg Ile Ser Pro Ser Ser Cys Leu Met Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Gln Glu Glu Phe Asp Gly Asn Gln Phe
        35                  40                  45

Gln Lys Ala Pro Ala Ile Ser Val Leu His Glu Leu Ile Gln Gln Ile
```

-continued

```
    50                  55                  60

Phe Asn Leu Phe Thr Thr Lys Asp Ser Ser Ala Ala Trp Asp Glu Asp
65                  70                  75                  80

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

Glu Ala Cys Val Met Gln Glu Glu Arg Val Gly Glu Thr Pro Leu Met
            100                 105                 110

Asn Ala Asp Ser Ile Leu Ala Val Lys Lys Tyr Phe Arg Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Leu Ser Leu Ser Thr Asn Leu Gln Glu
145                 150                 155                 160

Arg Leu Arg Arg Lys Glu
                165


<210> SEQ ID NO 19
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Cys Asp Leu Pro Gln Thr His Ser Leu Gly Asn Arg Arg Ala Leu Ile
1               5                   10                  15

Leu Leu Ala Gln Met Gly Arg Ile Ser His Phe Ser Cys Leu Lys Asp
            20                  25                  30

Arg His Asp Phe Gly Phe Pro Glu Glu Glu Phe Asp Gly His Gln Phe
        35                  40                  45

Gln Lys Ala Gln Ala Ile Ser Val Leu His Glu Met Ile Gln Gln Thr
    50                  55                  60

Phe Asn Leu Phe Ser Thr Glu Asp Ser Ser Ala Ala Trp Glu Gln Ser
65                  70                  75                  80

Leu Leu Glu Lys Phe Ser Thr Glu Leu Tyr Gln Gln Leu Asn Asp Leu
                85                  90                  95

Glu Ala Cys Val Ile Gln Glu Val Gly Val Glu Glu Thr Pro Leu Met
            100                 105                 110

Asn Glu Asp Ser Ile Leu Ala Val Arg Lys Tyr Phe Gln Arg Ile Thr
        115                 120                 125

Leu Tyr Leu Thr Glu Lys Lys Tyr Ser Pro Cys Ala Trp Glu Val Val
    130                 135                 140

Arg Ala Glu Ile Met Arg Ser Leu Ser Phe Ser Thr Asn Leu Gln Lys
145                 150                 155                 160

Arg Leu Arg Arg Lys Asp
                165


<210> SEQ ID NO 20
<211> LENGTH: 166
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln Arg Ser Ser Asn Phe Gln
1               5                   10                  15

Cys Gln Lys Leu Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr Cys Leu
```

-continued

```
            20                  25                  30

Lys Asp Arg Met Asn Phe Asp Ile Pro Glu Glu Ile Lys Gln Leu Gln
        35                  40                  45

Gln Phe Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr Glu Met Leu Gln
    50                  55                  60

Asn Ile Phe Ala Ile Phe Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn
65                  70                  75                  80

Glu Thr Ile Val Glu Asn Leu Leu Ala Asn Val Tyr His Gln Ile Asn
                85                  90                  95

His Leu Lys Thr Val Leu Glu Glu Lys Leu Glu Lys Glu Asp Phe Thr
            100                 105                 110

Arg Gly Lys Leu Met Ser Ser Leu His Leu Lys Arg Tyr Tyr Gly Arg
        115                 120                 125

Ile Leu His Tyr Leu Lys Ala Lys Glu Tyr Ser His Cys Ala Trp Thr
    130                 135                 140

Ile Val Arg Val Glu Ile Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu
145                 150                 155                 160

Thr Gly Tyr Leu Arg Asn
                165


<210> SEQ ID NO 21
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 21

Met Ala Leu Thr Phe Tyr Leu Leu Val Ala Leu Val Val Leu Ser Tyr
1               5                   10                  15

Lys Ser Phe Ser Ser Leu Gly
            20


<210> SEQ ID NO 22
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 22

Met Ala Arg Ser Phe Ser Leu Leu Met Val Val Leu Val Leu Ser Tyr
1               5                   10                  15

Lys Ser Ile Cys Ser Leu Gly
            20


<210> SEQ ID NO 23
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 23

Met Ala Leu Pro Phe Ala Leu Leu Met Ala Leu Val Val Leu Ser Cys
1               5                   10                  15
```

-continued

Lys Ser Ser Cys Ser Leu Asp
20

<210> SEQ ID NO 24
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 24

Met Ala Leu Ser Phe Ser Leu Leu Met Ala Val Leu Val Leu Ser Tyr
1 5 10 15

Lys Ser Ile Cys Ser Leu Gly
20

<210> SEQ ID NO 25
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 25

Met Ala Leu Thr Phe Ala Leu Leu Val Ala Leu Leu Val Leu Ser Cys
1 5 10 15

Lys Ser Ser Cys Ser Val Gly
20

<210> SEQ ID NO 26
<211> LENGTH: 557
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Met Met Val Val Leu Leu Gly Ala Thr Thr Leu Val Leu Val Ala Val
1 5 10 15

Ala Pro Trp Val Leu Ser Ala Ala Ala Gly Gly Lys Asn Leu Lys Ser
20 25 30

Pro Gln Lys Val Glu Val Asp Ile Ile Asp Asp Asn Phe Ile Leu Arg
35 40 45

Trp Asn Arg Ser Asp Glu Ser Val Gly Asn Val Thr Phe Ser Phe Asp
50 55 60

Tyr Gln Lys Thr Gly Met Asp Asn Trp Ile Lys Leu Ser Gly Cys Gln
65 70 75 80

Asn Ile Thr Ser Thr Lys Cys Asn Phe Ser Ser Leu Lys Leu Asn Val
85 90 95

Tyr Glu Glu Ile Lys Leu Arg Ile Arg Ala Glu Lys Glu Asn Thr Ser
100 105 110

Ser Trp Tyr Glu Val Asp Ser Phe Thr Pro Phe Arg Lys Ala Gln Ile
115 120 125

Gly Pro Pro Glu Val His Leu Glu Ala Glu Asp Lys Ala Ile Val Ile
130 135 140

His Ile Ser Pro Gly Thr Lys Asp Ser Val Met Trp Ala Leu Asp Gly
145 150 155 160

-continued

```
Leu Ser Phe Thr Tyr Ser Leu Val Ile Trp Lys Asn Ser Ser Gly Val
                165                 170                 175

Glu Glu Arg Ile Glu Asn Ile Tyr Ser Arg His Lys Ile Tyr Lys Leu
            180                 185                 190

Ser Pro Glu Thr Thr Tyr Cys Leu Lys Val Lys Ala Ala Leu Leu Thr
        195                 200                 205

Ser Trp Lys Ile Gly Val Tyr Ser Pro Val His Cys Ile Lys Thr Thr
    210                 215                 220

Val Glu Asn Glu Leu Pro Pro Pro Glu Asn Ile Glu Val Ser Val Gln
225                 230                 235                 240

Asn Gln Asn Tyr Val Leu Lys Trp Asp Tyr Thr Tyr Ala Asn Met Thr
                245                 250                 255

Phe Gln Val Gln Trp Leu His Ala Phe Leu Lys Arg Asn Pro Gly Asn
            260                 265                 270

His Leu Tyr Lys Trp Lys Gln Ile Pro Asp Cys Glu Asn Val Lys Thr
        275                 280                 285

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

Leu Arg Val Gln Ala Ser Asp Gly Asn Asn Thr Ser Phe Trp Ser Glu
305                 310                 315                 320

Glu Ile Lys Phe Asp Thr Glu Ile Gln Ala Phe Leu Leu Pro Pro Val
                325                 330                 335

Phe Asn Ile Arg Ser Leu Ser Asp Ser Phe His Ile Tyr Ile Gly Ala
            340                 345                 350

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

Tyr Glu Ile Ile Phe Trp Glu Asn Thr Ser Asn Ala Glu Arg Lys Ile
    370                 375                 380

Ile Glu Lys Lys Thr Asp Val Thr Val Pro Asn Leu Lys Pro Leu Thr
385                 390                 395                 400

Val Tyr Cys Val Lys Ala Arg Ala His Thr Met Asp Glu Lys Leu Asn
                405                 410                 415

Lys Ser Ser Val Phe Ser Asp Ala Val Cys Glu Lys Thr Lys Pro Gly
            420                 425                 430

Asn Thr Ser Lys Ile Trp Leu Ile Val Gly Ile Cys Ile Ala Leu Phe
        435                 440                 445

Ala Leu Pro Phe Val Ile Tyr Ala Ala Lys Val Phe Leu Arg Cys Ile
    450                 455                 460

Asn Tyr Val Phe Phe Pro Ser Leu Lys Pro Ser Ser Ser Ile Asp Glu
465                 470                 475                 480

Tyr Phe Ser Glu Gln Pro Leu Lys Asn Leu Leu Leu Ser Thr Ser Glu
                485                 490                 495

Glu Gln Ile Glu Lys Cys Phe Ile Ile Glu Asn Ile Ser Thr Ile Ala
            500                 505                 510

Thr Val Glu Glu Thr Asn Gln Thr Asp Glu Asp His Lys Lys Tyr Ser
        515                 520                 525

Ser Gln Thr Ser Gln Asp Ser Gly Asn Tyr Ser Asn Glu Asp Glu Ser
    530                 535                 540

Glu Ser Lys Thr Ser Glu Glu Leu Gln Gln Asp Phe Val
545                 550                 555
```

-continued

<210> SEQ ID NO 27
<211> LENGTH: 331
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Met Leu Leu Ser Gln Asn Ala Phe Ile Phe Arg Ser Leu Asn Leu Val
1 5 10 15

Leu Met Val Tyr Ile Ser Leu Val Phe Gly Ile Ser Tyr Asp Ser Pro
20 25 30

Asp Tyr Thr Asp Glu Ser Cys Thr Phe Lys Ile Ser Leu Arg Asn Phe
35 40 45

Arg Ser Ile Leu Ser Trp Glu Leu Lys Asn His Ser Ile Val Pro Thr
50 55 60

His Tyr Thr Leu Leu Tyr Thr Ile Met Ser Lys Pro Glu Asp Leu Lys
65 70 75 80

Val Val Lys Asn Cys Ala Asn Thr Thr Arg Ser Phe Cys Asp Leu Thr
85 90 95

Asp Glu Trp Arg Ser Thr His Glu Ala Tyr Val Thr Val Leu Glu Gly
100 105 110

Phe Ser Gly Asn Thr Thr Leu Phe Ser Cys Ser His Asn Phe Trp Leu
115 120 125

Ala Ile Asp Met Ser Phe Glu Pro Pro Glu Phe Glu Ile Val Gly Phe
130 135 140

Thr Asn His Ile Asn Val Met Val Lys Phe Pro Ser Ile Val Glu Glu
145 150 155 160

Glu Leu Gln Phe Asp Leu Ser Leu Val Ile Glu Glu Gln Ser Glu Gly
165 170 175

Ile Val Lys Lys His Lys Pro Glu Ile Lys Gly Asn Met Ser Gly Asn
180 185 190

Phe Thr Tyr Ile Ile Asp Lys Leu Ile Pro Asn Thr Asn Tyr Cys Val
195 200 205

Ser Val Tyr Leu Glu His Ser Asp Glu Gln Ala Val Ile Lys Ser Pro
210 215 220

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

Ser Ala Lys Ile Gly Gly Ile Ile Thr Val Phe Leu Ile Ala Leu Val
245 250 255

Leu Thr Ser Thr Ile Val Thr Leu Lys Trp Ile Gly Tyr Ile Cys Leu
260 265 270

Arg Asn Ser Leu Pro Lys Val Leu Arg Gln Gly Leu Ala Lys Gly Trp
275 280 285

Asn Ala Val Ala Ile His Arg Cys Ser His Asn Ala Leu Gln Ser Glu
290 295 300

Thr Pro Glu Leu Lys Gln Ser Ser Cys Leu Ser Phe Pro Ser Ser Trp
305 310 315 320

Asp Tyr Lys Arg Ala Ser Leu Cys Pro Ser Asp
325 330

<210> SEQ ID NO 28
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 28

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

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

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

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

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Arg His Pro Gly Leu Asn Trp Ala Pro Asp Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 29
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 29

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 30
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 30

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr

-continued

```
            20                  25                  30

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

Gly Ile Ile Asp Pro Ser Asp Ser Asp Thr Ala Tyr Ser Pro Ser Phe
    50                  55                  60

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Pro Gly Leu Asn Trp Ala Pro Asp Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 31
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 31

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

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

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

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

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Pro Gly Leu Ala Trp Ala Pro Asp Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 32
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 32

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
```

-continued

```
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 33
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 33

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 34
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 34

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

-continued

<210> SEQ ID NO 35
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 35

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 36
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 36

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 37
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 37

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

-continued

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asp Glu Phe
            20                  25                  30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 38
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 38

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 39
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 39

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

-continued

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 40
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 40

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ala Glu Phe
            20                  25                  30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 41
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 41

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 42
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
```

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 42

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 43
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 43

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asp Asp Phe
20 25 30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 44
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 44

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

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

-continued

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 45
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 45

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 46
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 46

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

-continued

```
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 47
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 47

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 48
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 48

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Glu Phe
            20                  25                  30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 49
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
```

-continued

<400> SEQUENCE: 49

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 50
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 50

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Glu Tyr
20 25 30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 51
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 51

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

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

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

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

-continued

```
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 52
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 52

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 53
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 53

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

-continued

<210> SEQ ID NO 54
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 54

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ala Asp Phe
20 25 30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 55
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 55

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 56
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 56

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

-continued

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

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

Lys Trp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 57
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 57

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

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

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

Ile His Trp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

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

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

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 58
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 58

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

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

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

Trp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

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

-continued

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Asp Thr Pro Phe Thr
85 90 95

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 59
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 59

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

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

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

Ile His Trp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 60
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 60

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

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

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

Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Ile Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 61
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 61

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

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

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

Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 62
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 62

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

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

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

Ile His Trp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 63
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 63

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

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

-continued

```
Asn Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 64
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 64

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

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

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

Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 65
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 65

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asn Tyr Leu
            20                  25                  30

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

Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

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

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

-continued

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 66
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 66

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

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

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

Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 67
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 67

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

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

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

Ile His Trp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 68
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

-continued

<400> SEQUENCE: 68

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

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

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

Ile His Trp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 69
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 69

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

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

Asp Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
35 40 45

Ile His Trp Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 70
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 70

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

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

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

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

-continued

```
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 71
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 71

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 72
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 72

gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc     60

attacctgcc gcgcgagcca gagcattgat gggttcctga actggtatca gcagaaaccg    120

ggcaaagcgc cgaaactgct gatttatttc gcgagcagcc tgcagagcgg cgtgccgagc    180

cgctttagcg gcagcggcag cggcaccgat ttttaccctga ccattagcag cctgcagccg    240

gaagattttg cgacctatta ttgccagcag tcctacgacc tcccgattac atttggccag    300

ggcaccaaag tggaaattaa a                                               321


<210> SEQ ID NO 73
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 73
```

-continued

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 74
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 74

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Tyr
            20                  25                  30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 75
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 75

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

-continued

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 76
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 76

Gln Ser Ile Ala Asp Phe
1 5

<210> SEQ ID NO 77
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 77

Gln Ser Ile Ala Glu Phe
1 5

<210> SEQ ID NO 78
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 78

Gln Ser Ile Ala Asn Asn Asn
1 5

<210> SEQ ID NO 79
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 79

Gln Ser Ile Ala Asn Thr Asn
1 5

<210> SEQ ID NO 80
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 80

-continued

Gln Ser Ile Asp Gly Ala
1 5

<210> SEQ ID NO 81
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 81

Gln Ser Ile Asp Gly Phe
1 5

<210> SEQ ID NO 82
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 82

Gln Ser Ile Asp Asn Ser Tyr
1 5

<210> SEQ ID NO 83
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 83

Gln Ser Ile Asp Arg Ala
1 5

<210> SEQ ID NO 84
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 84

Gln Ser Ile Glu Gly Ala
1 5

<210> SEQ ID NO 85
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 85

Gln Ser Ile Gly Asp Phe
1 5

<210> SEQ ID NO 86

-continued

<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 86

Gln Ser Ile Gly Lys Ser
1 5

<210> SEQ ID NO 87
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 87

Gln Ser Ile Gly Ser Ala
1 5

<210> SEQ ID NO 88
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 88

Gln Ser Ile Asn Gly Val
1 5

<210> SEQ ID NO 89
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 89

Gln Ser Ile Arg Asn Thr Asn
1 5

<210> SEQ ID NO 90
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 90

Gln Ser Ile Ser Ser Ala
1 5

<210> SEQ ID NO 91
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

-continued

<400> SEQUENCE: 91

Gln Ser Ile Ser Ser Phe
1 5

<210> SEQ ID NO 92
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 92

gacatccaaa tgacgcagtc tccgagctct ctgagcgcat ccgtgggcga tcgcgtaact 60

atcacttgtc gcgcctccca gagcattgat aactcctatc tcaattggta tcaacaaaaa 120

ccgggtaagg caccgaaact gctgatttac ggagcgtcct ctctgcagtc cggtgtgccg 180

tcccgtttct ccggcagcgg ttctggtacc gatttcacgc tgaccatcag ctctctgcaa 240

ccggaggact ttgctacgta ctactgccaa cagggctacg atttccctct cacattcggc 300

caaggtacca aagtggaaat taaa 324

<210> SEQ ID NO 93
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 93

Phe Ala Ser
1

<210> SEQ ID NO 94
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 94

Gly Ala Ser
1

<210> SEQ ID NO 95
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 95

Trp Ala Ser
1

<210> SEQ ID NO 96
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

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

<400> SEQUENCE: 96

Gln Gln Ala Leu Asp Phe Pro Leu Thr
1 5

<210> SEQ ID NO 97
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 97

Gln Gln Ala Tyr Asp Phe Pro Leu Thr
1 5

<210> SEQ ID NO 98
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 98

Gln Gln Gly Trp Asp Trp Pro Leu Thr
1 5

<210> SEQ ID NO 99
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 99

Gln Gln Gly Tyr Asp Phe Pro Leu Thr
1 5

<210> SEQ ID NO 100
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 100

Gln Gln Gly Tyr Asp Thr Pro Phe Thr
1 5

<210> SEQ ID NO 101
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 101

-continued

Gln Gln Ser Phe Asp Phe Pro Leu Thr
1 5

<210> SEQ ID NO 102
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 102

Gln Gln Ser His Asp Phe Pro Leu Thr
1 5

<210> SEQ ID NO 103
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 103

Gln Gln Ser His Ser Phe Pro Leu Thr
1 5

<210> SEQ ID NO 104
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 104

Gln Gln Ser Ile Asp Phe Pro Leu Thr
1 5

<210> SEQ ID NO 105
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 105

Gln Gln Ser Tyr Asp Phe Pro Leu Thr
1 5

<210> SEQ ID NO 106
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 106

Gln Gln Ser Tyr Asp Leu Pro Ile Thr
1 5

<210> SEQ ID NO 107
<211> LENGTH: 9

-continued

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

<400> SEQUENCE: 107

Gln Gln Trp Tyr Asp Asn Pro Leu Thr
1 5

<210> SEQ ID NO 108
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 108

gatattcaga tgacccagag cccgagcagc ctgagcgcga gcgtgggcga tcgcgtgacc 60

attacctgcc gcgcgagcca gagcatcgat ggcgccctga actggtatca gcagaaaccg 120

ggcaaagcgc cgaaactgct gatttatttc gcgagcagcc tgcagagcgg cgtgccgagc 180

cgctttagcg gcagcggcag cggcaccgat tttaccctga ccattagcag cctgcagccg 240

gaagattttg cgacctatta ttgccagcag gcctacgact ttccgttgac atttggccag 300

ggcaccaaag tggaaattaa a 321

<210> SEQ ID NO 109
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 109

Gly Tyr Ser Phe Thr Ser Tyr Trp
1 5

<210> SEQ ID NO 110
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 110

gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgagag cctgaagatc 60

agctgcaagg gcagcggcta cagcttcacc agctactgga tcggctgggt gcggcagatg 120

cccggcaagg gcctggagtg gatgggcatc atcgacccca gcgacagcga cacccggtac 180

agccccagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240

ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc ccggcacccc 300

ggcctgaact gggcccccga cttcgactac tggggccagg gcaccctggt gaccgtgagc 360

agc 363

<210> SEQ ID NO 111
<211> LENGTH: 8

-continued

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

<400> SEQUENCE: 111

Ile Ala Pro Ser Asp Ser Asp Thr
1 5

<210> SEQ ID NO 112
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 112

Ile Asp Ala Ser Asp Ser Asp Thr
1 5

<210> SEQ ID NO 113
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 113

Ile Asp Pro Ser Asp Ser Asp Thr
1 5

<210> SEQ ID NO 114
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Asp or Ala
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Pro or Ala

<400> SEQUENCE: 114

Ile Xaa Xaa Ser Asp Ser Asp Thr
1 5

<210> SEQ ID NO 115
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 115

Ala Arg His Pro Gly Leu Ala Trp Ala Pro Asp Phe Asp Tyr
1 5 10

-continued

<210> SEQ ID NO 116
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 116

Ala Arg His Pro Gly Leu Asn Trp Ala Pro Asp Phe Asp Tyr
1 5 10

<210> SEQ ID NO 117
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 117

gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgagag cctgaagatc 60

agctgcaagg gcagcggcta cagcttcacc agctactgga tcggctgggt gcggcagatg 120

cccggcaagg gcctggagtg gatgggcatc atcgacgcca gcgacagcga cacccggtac 180

agccccagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240

ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc ccggcacccc 300

ggcctgaact gggcccccga cttcgactac tggggccagg gcaccctggt gaccgtgagc 360

agc 363

<210> SEQ ID NO 118
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Gly, Asp, Ala, Arg, Glu, Ser or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Asp, Gly, Asn, Ser, Arg, Glu or Lys
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Phe, Ala, Asn, Thr, Ser or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Tyr, Asn or not present

<400> SEQUENCE: 118

Gln Ser Ile Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 119
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

-continued

<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Phe, Trp or Gly

<400> SEQUENCE: 119

Xaa Ala Ser
1

<210> SEQ ID NO 120
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Ala, Gly, Ser or Trp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Leu, Tyr, His, Trp, Phe or Ile
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Asp or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Phe, Thr, Leu, Asn or Trp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Leu, Phe or Ile

<400> SEQUENCE: 120

Gln Gln Xaa Xaa Xaa Xaa Pro Xaa Thr
1 5

<210> SEQ ID NO 121
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Ala or Asn

<400> SEQUENCE: 121

Ala Arg His Pro Gly Leu Xaa Trp Ala Pro Asp Phe Asp Tyr
1 5 10

<210> SEQ ID NO 122
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 122

gaggtgcagc tggtgcagag cggcgccgag gtgaagaagc ccggcgagag cctgaagatc 60

agctgcaagg gcagcggcta cagcttcacc agctactgga tcggctgggt gcggcagatg 120

-continued

cccggcaagg gcctggagtg gatgggcatc atcgacccca gcgacagcga cacccggtac 180

agccccagct tccagggcca ggtgaccatc agcgccgaca agagcatcag caccgcctac 240

ctgcagtgga gcagcctgaa ggccagcgac accgccatgt actactgcgc ccggcacccc 300

ggcctggcct gggcccccga cttcgactac tggggccagg gcaccctggt gaccgtgagc 360

agc 363

<210> SEQ ID NO 123
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 123

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 124
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 124

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Phe
20 25 30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

-continued

<210> SEQ ID NO 125
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 125

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 126
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 126

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 127
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 127

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

-continued

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Asp Gly Phe
            20                  25                  30

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

Tyr Ile Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 128
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 128

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

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

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

Tyr Leu Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 129
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 129

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

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

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

Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

-continued

```
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Asp Leu Pro Ile
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 130
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 130

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Tyr
            20                  25                  30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 131
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 131

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Phe
            20                  25                  30

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 132
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
```

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 132

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Phe
20 25 30

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

Tyr Ile Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 133
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 133

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Phe
20 25 30

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

Tyr Leu Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 134
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 134

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Phe
20 25 30

-continued

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

Tyr Val Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 135
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 135

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Phe
            20                  25                  30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 136
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 136

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Asp Leu Pro Ile
                85                  90                  95
```

-continued

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 137
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 137

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

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

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

Tyr Tyr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 138
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 138

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Tyr
20 25 30

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

Tyr Tyr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 139
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

-continued

<400> SEQUENCE: 139

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Glu Gly Phe
20 25 30

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

Tyr Tyr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 140
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 140

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Phe
20 25 30

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

Tyr Tyr Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 141
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 141

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

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

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

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

-continued

```
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 142
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 142

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 143
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 143

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

-continued

<210> SEQ ID NO 144
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 144

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 145
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 145

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

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

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 146
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 146

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

-continued

```
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30

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

Tyr Phe Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 147
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 147

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 148
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 148

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

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

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

Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

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

-continued

```
Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Asp Trp Pro
                85                  90                  95

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 149
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 149

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

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

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

Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 150
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 150

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

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

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

Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 151
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
```

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 151

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

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

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

Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 152
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 152

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

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

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

Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 153
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 153

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

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

-continued

```
Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
    50                  55                  60

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

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

Leu Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 154
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 154

Gln Gln Ser Tyr Asp Phe Pro Leu
1               5


<210> SEQ ID NO 155
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

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

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

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

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

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg


<210> SEQ ID NO 156
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
```

-continued

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 157
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 157

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

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

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

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

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Pro Gly Leu Asn Trp Ala Pro Asp Phe Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 158
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 158

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

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

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

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

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

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg His Pro Gly Leu Asn Trp Ala Pro Asp Phe Asp Tyr Trp Gly
            100                 105                 110
```

-continued

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 159
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Gly, Asp, Ala, Glu, Ser or Asn
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Asp, Gly, Asn, Ser or Arg
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Phe, Ala, Asn, Ser or Val
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Tyr, Asn or not present

<400> SEQUENCE: 159

Gln Ser Ile Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 160
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Ala, Gly or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Tyr, His, Trp or Phe
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Asp or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Phe, Thr, Leu or Trp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Leu, Phe or Ile

<400> SEQUENCE: 160

Gln Gln Xaa Xaa Xaa Xaa Pro Xaa Thr
1 5

<210> SEQ ID NO 161
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

-continued

```
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Ala or Asp
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Asn or Gly
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Phe, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Tyr, Asn or not present

<400> SEQUENCE: 161

Gln Ser Ile Xaa Xaa Xaa Xaa
1               5


<210> SEQ ID NO 162
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Gly or Ser
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Phe, Thr or Leu
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Leu, Phe or Ile

<400> SEQUENCE: 162

Gln Gln Xaa Tyr Asp Xaa Pro Xaa Thr
1               5
```

We claim:

1) An isolated monoclonal antibody that binds to and neutralizes a biological activity of a human interferon omega (IFN-ω) and at least three, four, five, six, seven, eight, nine, ten or eleven human interferon alpha (IFN-α) subtypes.

2) The antibody of claim **1**, wherein the biological activity of the human IFN-ω and the human INF-α subtypes is the human IFN-ω or the human INF-α subtype-induced expression of secreted embryonic alkaline phosphatase (SEAP) under interferon inducible ISG54 promoter in HEK293 cells stably expressing signal transducer and activator of transcription 2 (STAT2), interferon regulatory factor 9 (IRF9) and SEAP.

3) The antibody of claim **2**, wherein the antibody neutralizes the biological activity of the human IFN-ω with an IC_{50} value of at least about 1×10^{-9}M or less, about 1×10^{-10} M or less, about 5×10^{-11}M or less, or about 1×10^{-11}M or less.

4) The antibody of claim **3**, wherein the antibody neutralizes the biological activity of the human IFN-co with an IC_{50} value of at least about 1×10^{-10} M or less.

5) The antibody of claim **4**, wherein the antibody neutralizes the activity of the human IFN-ω with an IC_{50} value of between about 1×10^{-10} M to about 6×10^{-12}M.

6) The antibody of claim **5**, wherein the antibody neutralizes the activity of at least three, four, five, six, seven, eight, nine, ten or eleven human INF-α subtypes with an IC_{50} value of at least about 2×10^{-10} M or less, about 1.5×10^{-10} M or less, or about 1×10^{-10} M or less.

7) The antibody of claim **6**, wherein the INF-α subtypes are selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJI, IFN-αK, IFN-αWA and IFN-α4a.

8) The antibody of claim **6**, comprising

a) the HCDR1 amino acid sequence of SEQ ID NO: 109;

b) the HCDR2 amino acid sequences of SEQ ID NOs: 111, 112 or 113;

c) the HCDR3 amino acid sequences of SEQ ID NOs: 115 or 116;

d) the LCDR1 amino acid sequences of SEQ ID NOs: 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91;

e) the LCDR2 amino acid sequences of SEQ ID NOs: 93, 94 or 95; and

f) the LCDR3 amino acid sequences of SEQ ID NOs: 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106 or 107.

9) The antibody of claim **8**, wherein the antibody comprises heavy chain complementarity determining region (HCDR) 1 (HCDR1), 2 (HCDR2) and 3 (HCDR3) amino acid sequences of SEQ ID NOs: 109, 113 and 116, respectively, and light chain complementarity determining region (LCDR) 1 (LCDR1), 2 (LCDR2) and 3 (LCDR3) amino acid sequences of SEQ ID NOs: 82, 94 and 99, respectively.

10) The antibody of claim **6**, wherein the antibody comprises heavy chain complementarity determining region (HCDR) 1 (HCDR1), 2 (HCDR2) and 3 (HCDR3) amino acid sequences of SEQ ID NOs: 109, 114 and 121, respectively, and light chain complementarity determining region (LCDR) 1 (LCDR1), 2 (LCDR2) and 3 (LCDR3) amino acid sequences of SEQ ID NOs: 118, 119 and 120, respectively.

11) The antibody of claim **6**, wherein the antibody neutralizes at least six human INF-α subtypes selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJI, IFN-αK, IFN-αWA and IFN-α4a.

12) The antibody of claim **11**, wherein the antibody comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 114, 121, 159, 119 and 160, respectively.

13) The antibody of claim **6**, wherein the antibody neutralizes at least ten human INF-α subtypes selected from the group consisting of IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αI, IFN-αJI, IFN-αK, IFN-αWA and IFN-α4a.

14) The antibody of claim **13**, wherein the antibody binds human IFN-ω of SEQ ID NO: 1 at least at amino acid residues F27, L30 and R33.

15) The antibody of claim **14**, wherein the antibody comprises the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 amino acid sequences of SEQ ID NOs: 109, 114, 121, 161, 119 and 162, respectively.

16) The antibody of claim **15**, wherein the antibody neutralizes at least the human INF-α subtypes IFN-αA, IFN-αB2, IFN-αC, IFN-αF, IFN-αG, IFN-αH2, IFN-αJI and IFN-α4a.

17) The antibody of claim **16**, wherein the antibody further neutralizes IFN-cd, IFN-αK or IFN-αWA.

18) The antibody of claim **14**, wherein the antibody

a) inhibits leukocyte interferon-induced IP-10 release in whole blood induced by 250U/ml of interferon by about 50% or more in the presence of 10 μg/ml antibody than in the absence of the antibody; or

b) inhibits systemic lupus erythematosus (SLE) immune complex-induced IP-10 release in whole blood by about 50% or more in the presence of 10 μg/ml antibody than in the absence of the antibody.

19) The antibody of claim **5**, wherein the antibody comprises a heavy chain variable region (VH) amino acid sequence at least 90%, 95% or 97% identical to SEQ ID NO: 28 and a light chain variable region (VL) amino acid sequences at least 90%, 95% or 97% identical to SEQ ID NO: 150.

20) The antibody of claim **19**, comprising the HCDR1, the HCDR2, the HCDR3, the LCDR1, the LCDR2 and the LCDR3 sequences of SEQ ID NOs:

a) 109, 113, 116, 77, 93 and 104, respectively;
b) 109, 113, 116, 85, 93 and 96, respectively;
c) 109, 113, 115, 79, 95 and 107, respectively;
d) 109, 113, 116, 76, 93 and 103, respectively;
e) 109, 113, 115, 85, 93 and 96, respectively;
f) 109, 113, 115, 89, 95 and 100, respectively;
g) 109, 113, 116, 86, 93 and 105, respectively;
h) 109, 113, 115, 76, 93 and 103, respectively;
i) 109, 113, 116, 80, 93 and 97, respectively;
j) 109, 113, 116, 84, 93 and 97, respectively;
k) 109, 113, 116, 90, 93 and 97, respectively;
l) 109, 113, 116, 88, 93 and 102, respectively;
m) 109, 113, 116, 87, 93 and 105, respectively;
n) 109, 113, 116, 91, 93 and 106, respectively;
o) 109, 113, 115, 80, 93 and 97, respectively;
p) 109, 113, 116, 83, 93 and 101, respectively;
q) 109, 113, 116, 82, 94 and 98, respectively;
r) 109, 113, 115, 78, 95 and 100, respectively;
s) 109, 111, 116, 81, 93 and 106, respectively;
t) 109, 113, 116, 82, 94 and 99, respectively;
u) 109, 113, 115, 81, 93 and 106, respectively;
v) 109, 112, 116, 81, 93 and 106, respectively; or
w) 109, 113, 116, 81, 93 and 106, respectively.

21) The antibody of claim **20**, wherein the antibody is humanized or human.

22) The antibody of claim **21**, wherein the human antibody heavy chain variable region framework is derived from human germline gene IGHV5-51 (SEQ ID NO: 155).

23) The antibody of claim **22**, wherein the human antibody light chain variable region framework is derived from human germline gene IGKV1D-39 (SEQ ID NO: 156).

24) The antibody of claim **21**, wherein the antibody is of IgG1, IgG2, IgG3 or IgG4 subtype.

25) The antibody of claim **24**, wherein the antibody has at least one substitution in an Fc region.

26) The antibody of claim **25**, wherein the wherein the substitution comprises a substitution M252Y/S254T/T256E, V234A/G237A/P238S/H28AN309L/A330S/P331S or P238S/L234A/L235A, wherein residue numbering is according to the EU numbering.

27) The antibody of claim **19** comprising a heavy chain variable region (VH) and a light chain variable region (VL), wherein the

a) VH comprises the amino acid sequence of SEQ ID NOs: 28, 31, 157 or 158.

28) The antibody of claim **27**, wherein the VL comprises the amino acid sequence of SEQ ID NOs: 35, 39, 40, 42, 46, 52, 53, 54, 57, 61, 62, 68, 71, 73, 75, 135 or 150.

29) The antibody of claim **28** comprising the VH and the VL of SEQ ID NOs:

a) 28 and 40, respectively;
b) 28 and 39, respectively;
c) 31 and 62, respectively;
d) 28 and 54, respectively;
e) 31 and 39, respectively;
f) 31 and 68, respectively;
g) 28 and 42, respectively;
h) 31 and 54, respectively;
i) 28 and 53, respectively;
j) 28 and 73, respectively;
k) 28 and 75, respectively;
l) 28 and 52, respectively;
m) 28 and 35, respectively;
n) 28 and 135, respectively;
o) 31 and 53, respectively;
p) 28 and 46, respectively;
q) 28 and 61, respectively;

r) 31 and 57, respectively;
s) 157 and 71, respectively;
t) 28 and 150, respectively;
u) 31 and 71, respectively;
v) 158 and 71, respectively; or
w) 28 and 71, respectively.

30) The antibody of claims **19**, comprising a VH amino acid sequence of SEQ ID NO: 28 and a VL amino acid sequence of SEQ ID NO: 150.

31) The antibody of claim **29**, wherein the antibody is bispecific.

32) The antibody of claim **31**, wherein the antibody binds BLyS, CD40L, IL-6, CD27, BDCA2, IL-12, IL-23, IFN-αD, IL-17, CD20, IL-10, CD22, IL-21, ICOS, ICOSL or IFN-γ.

33) A pharmaceutical composition comprising the antibody of claim **29** and a pharmaceutically accepted carrier.

34) A polynucleotide encoding the antibody VH or VL of claim **29**, or (ii) the antibody VH and VL of claim **29**.

35) A vector comprising the polynucleotide of claim **34**.

36) A host cell comprising the vector of claim **35**.

37) A method of producing an antibody, comprising culturing the host cell of claim **36** in conditions that the antibody is expressed, and recovering the antibody produced by the host cell.

38) A method of treating an immune-mediated inflammatory disease, an autoimmune disease or chronic viral infection, comprising administering a therapeutically effective amount of the isolated antibody of claim **29** to a patient in need thereof for a time sufficient to treat the disease or the infection.

39) The method of claim **38**, wherein the immune-mediated inflammatory disease or the autoimmune disease is lupus, psoriasis, immune thrombocytopenia (ITP), Aicardi-Goutieres syndrome (AGS), systemic sclerosis, Sjogren's syndrome, myositis, common variable immune deficiency (CVID), autoimmune thyroid disease, type I diabetes, rheumatoid arthritis, transplant rejection or graft versus host disease (GVHD).

40) The method of claim **39**, wherein lupus is systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE).

41) The method of claim **40**, wherein the patient has lupus nephritis.

42) The method of claim **38**, wherein the patient exhibits a Type I interferon signature.

43) The method of claim **38**, wherein the chronic viral infection is HIV or hepatitis C infection.

44) The method of claim **38**, wherein the antibody comprises the antibody of claim **20** or **29**.

45) The method of claim **38**, wherein the antibody is a bispecific antibody. 46) The method of claim **45**, wherein the bispecific antibody neutralizes BLyS, CD40L, IL-6, CD27, BDCA2, IL-12, IL-23, IFN-αD, IL-17, CD20, IL-10, CD22, IL-21, ICOS, ICOSL or IFN-γ.

47) The method of claim **38**, further administering a second therapeutic agent. 48) The method of claim **47**, wherein the second therapeutic agent is an antibody that binds BLyS, CD4OL, IL-6, CD27, BDCA2, IL-12, IL-23, IFN-αD, IL-17, CD20, IL-10, CD22, IL-21, ICOS, ICOSL or IFN-γ.

49) The method of claim **47**, wherein the second therapeutic agent is a corticosteroid, an antimalarial drug, an immunosuppressant, a cytotoxic drug, or a B-cell modulator.

50) The method of claim **49**, wherein the second therapeutic agent is prednisone, prednisolone, methylprednisolone, deflazcort, hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil (MMF), mycophenolate sodium, cyclosporine, leflunomide, tacrolimus, rituximabTM or belimumab™.

51) The antibody of claim **32**, wherein the antibody does not neutralize IFN-αD, IFN-α1 and/or IFN-β.

* * * * *