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Foltz et al.

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(45) **Date of Patent: Apr. 19, 2016**

(54) **ANTI-HEPCIDIN ANTIBODIES AND METHODS OF USE**

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(73) Assignee: **AMGEN INC.**, Thousand Oaks, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 357 days.

(21) Appl. No.: **12/990,137**

(22) PCT Filed: **Apr. 28, 2009**

(86) PCT No.: **PCT/US2009/002606**

§ 371 (c)(1),
(2), (4) Date: **Feb. 11, 2011**

(87) PCT Pub. No.: **WO2009/139822**

PCT Pub. Date: **Nov. 19, 2009**

(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Provisional application No. 61/049,687, filed on May 1, 2008.

(51) **Int. Cl.**

C07K 16/26	(2006.01)
A61K 38/18	(2006.01)
A61K 39/395	(2006.01)
A61K 39/00	(2006.01)
C07K 19/00	(2006.01)

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

CPC ***C07K 16/26*** (2013.01); ***A61K 38/1816*** (2013.01); ***A61K 39/3955*** (2013.01); *A61K 2039/505* (2013.01); *C07K 2317/21* (2013.01); *C07K 2317/56* (2013.01); *C07K 2317/565* (2013.01); *C07K 2317/76* (2013.01); *C07K 2317/77* (2013.01); *C07K 2317/92* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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* cited by examiner

Primary Examiner — Daniel E Kolker

Assistant Examiner — James Rogers

(74) *Attorney, Agent, or Firm* — Susan Lingenfelter; Jonathan M. Dermott

(57) **ABSTRACT**

The invention relates to monoclonal antibodies that bind hepcidin and methods of making and using such antibodies. Also provided are methods of treating hepcidin-related disorders.

2 Claims, 26 Drawing Sheets

FIG. 1A

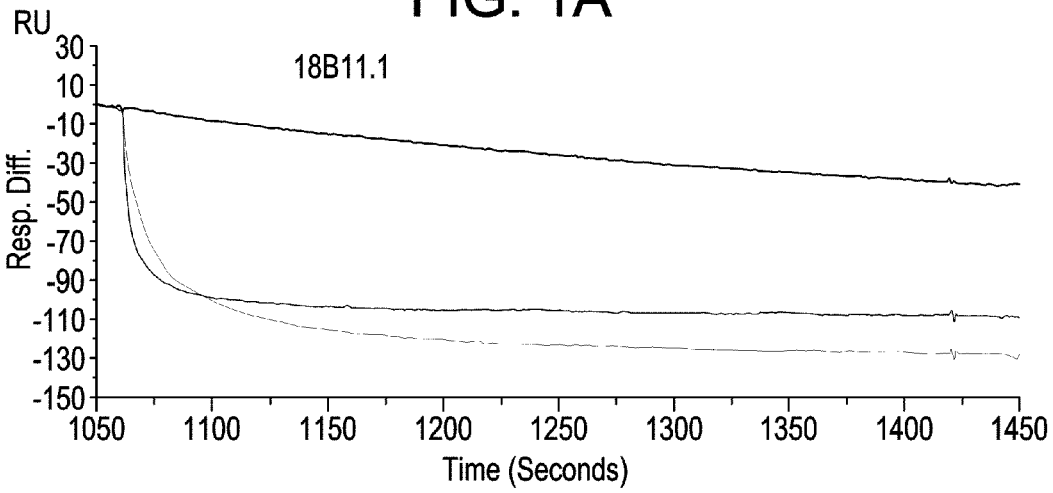


FIG. 1B

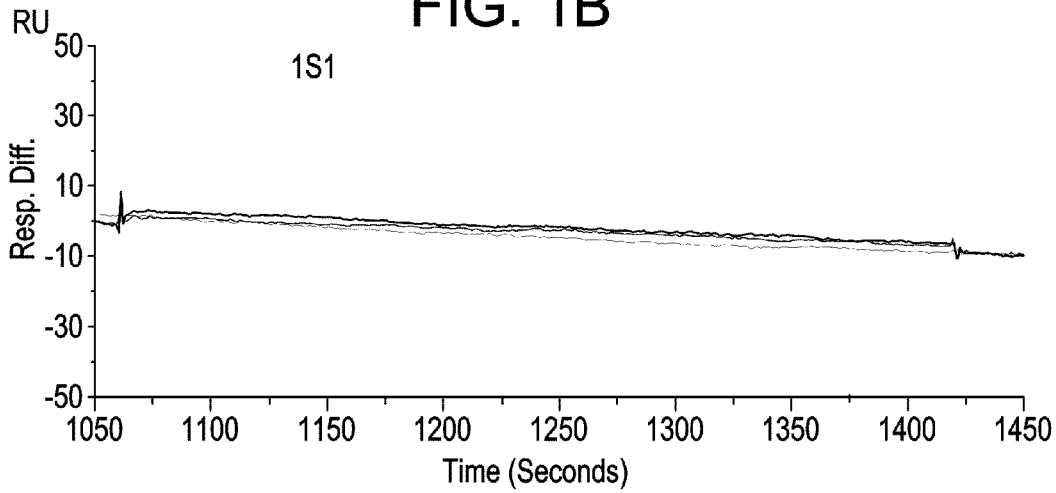


FIG. 1C

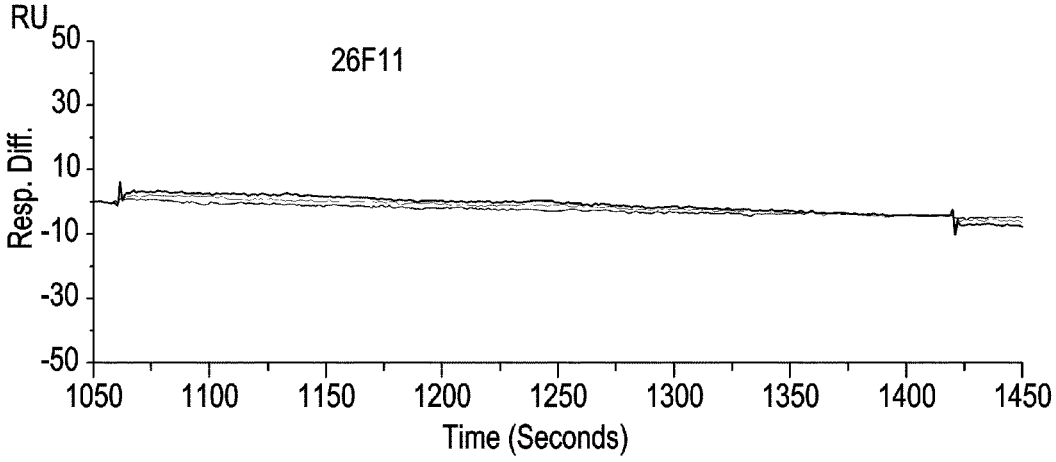


FIG. 1D

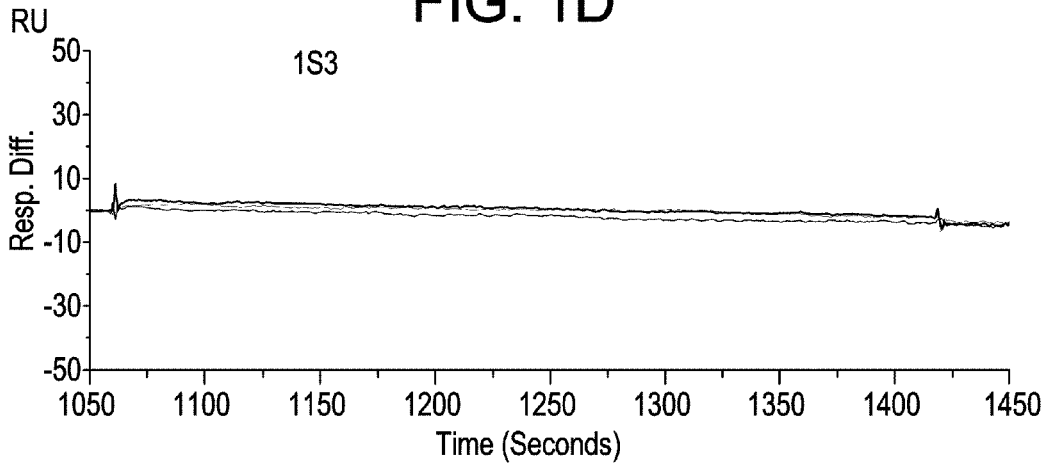


FIG. 1E

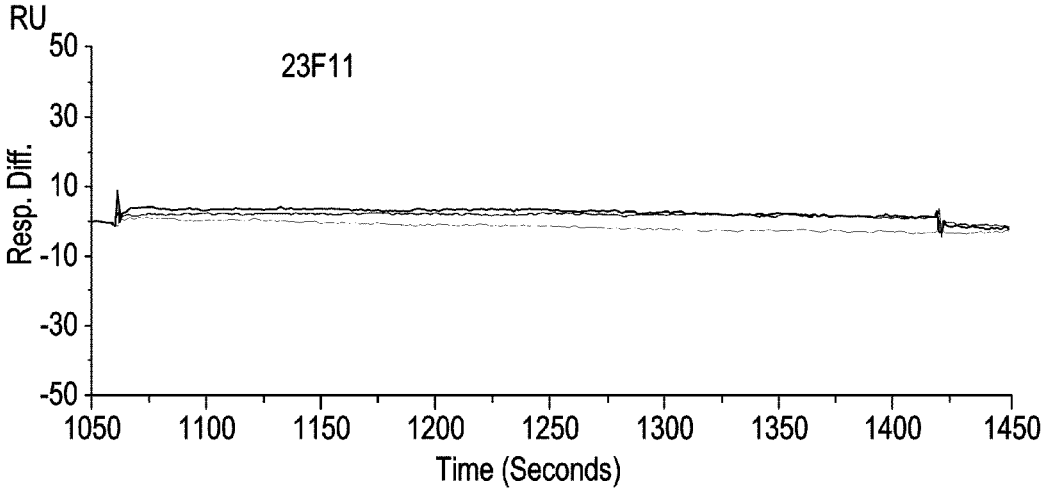


FIG. 1F

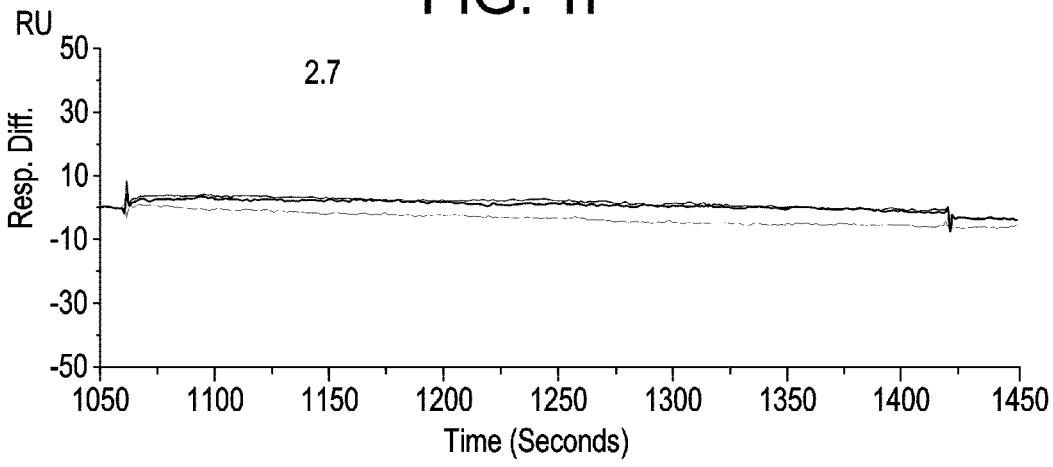


FIG. 2

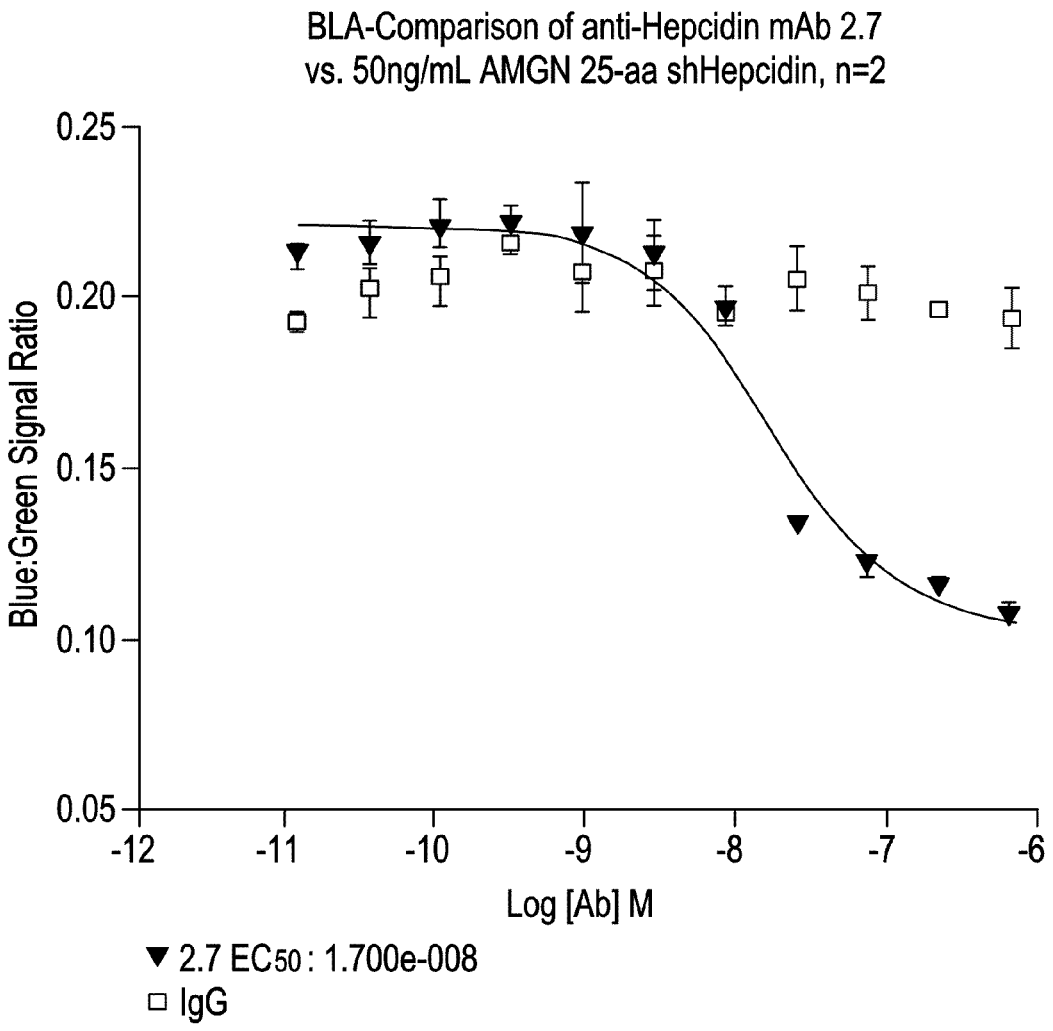

BLA-Comparison of anti-Hepcidin mAb 2.7
vs. 50ng/mL AMGN 25-aa shHepcidin, n=2
Blue:Green Signal Ratio
0.25
0.20
0.15
0.10
0.05
-12
-11
-10
-9
-8
-7
-6
Log [Ab] M
▼ 2.7 EC50 : 1.700e-008
□ IgG

FIG. 3

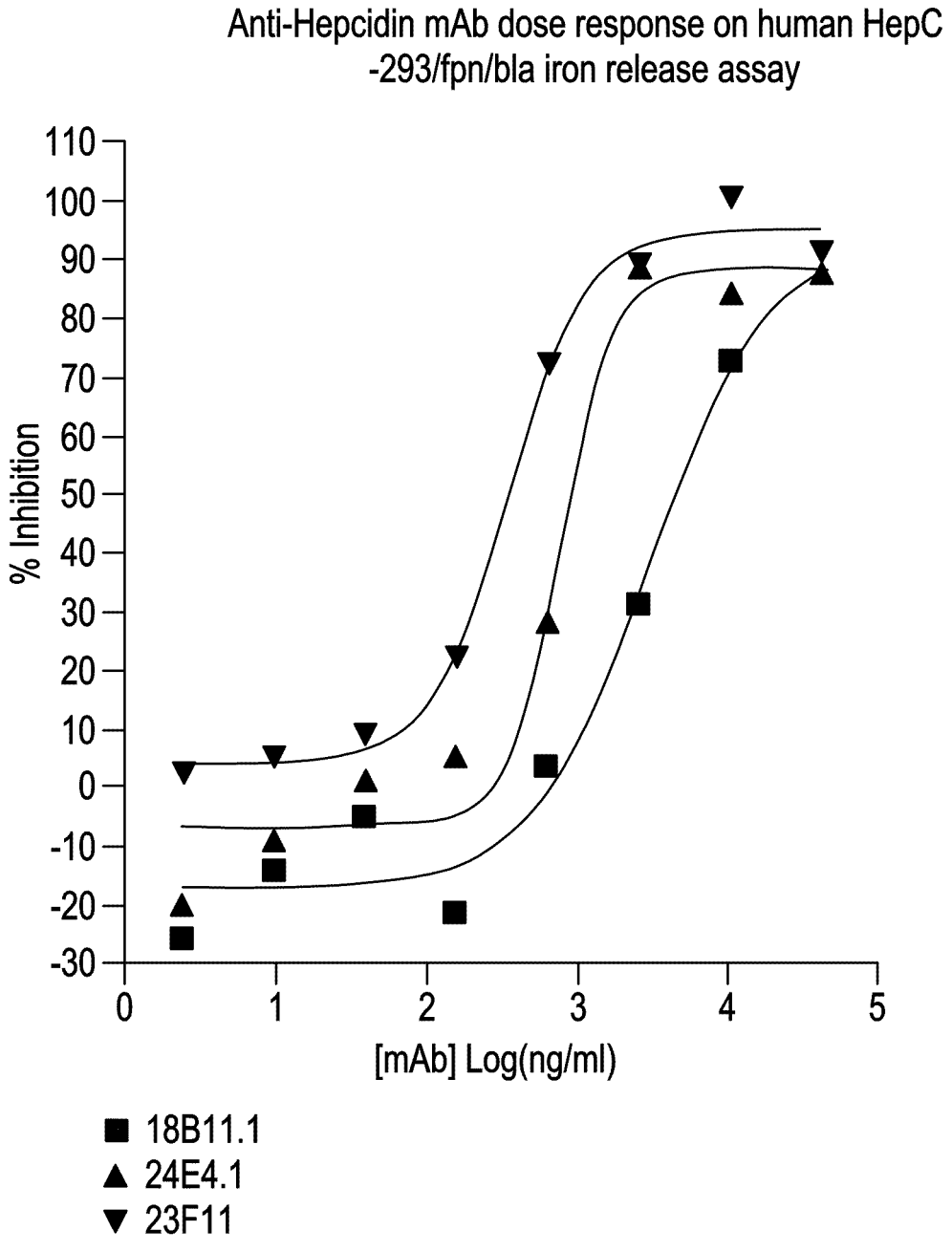

Anti-Hepcidin mAb dose response on human HepC
-293/fpn/bla iron release assay
% Inhibition
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
0
1
2
3
4
5
[mAb] Log(ng/ml)
18B11.1
24E4.1
23F11

FIG. 4A

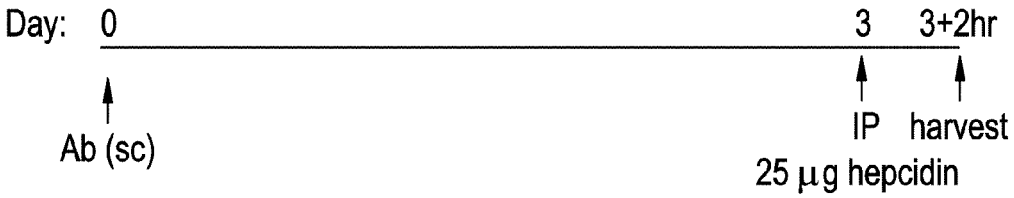

Day: 0
3
3+2hr
Ab (sc)
IP
harvest
25 μg hepcidin

FIG. 4B

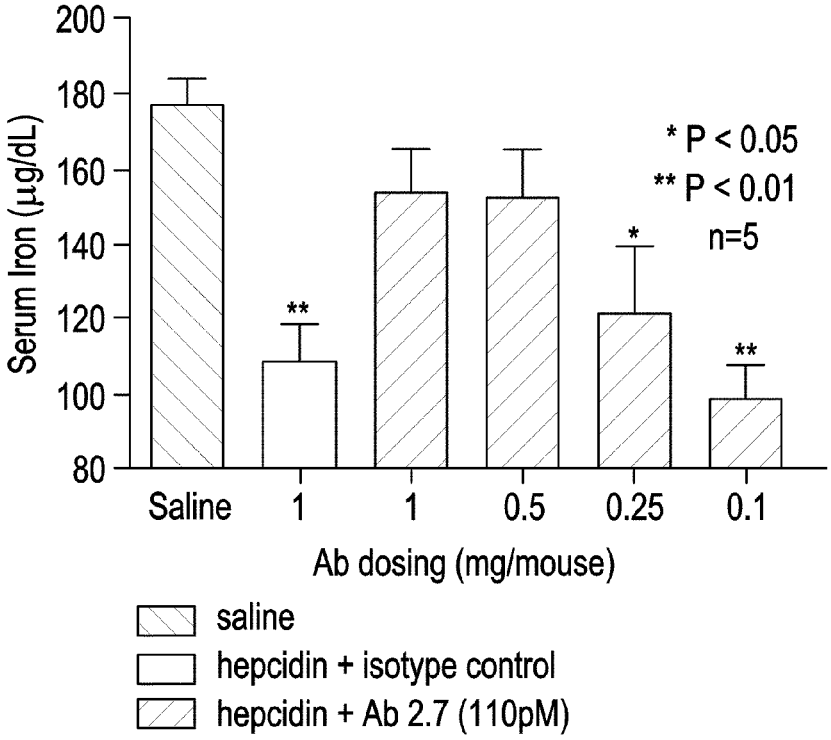

200
180
160
140
120
100
80
Serum Iron (μg/dL)
* P < 0.05
** P < 0.01
n=5
**
*
**
Saline
1
1
0.5
0.25
0.1
Ab dosing (mg/mouse)
saline
hepcidin + isotype control
hepcidin + Ab 2.7 (110pM)

FIG. 5A


Week: 0
1
2
3
Virus delivered
(tail vein)
β-gal control
or human hepcidin
Ab 4X: M T W Th Fri
(harvest)
Ab 2X: M W
Ab 1X: M

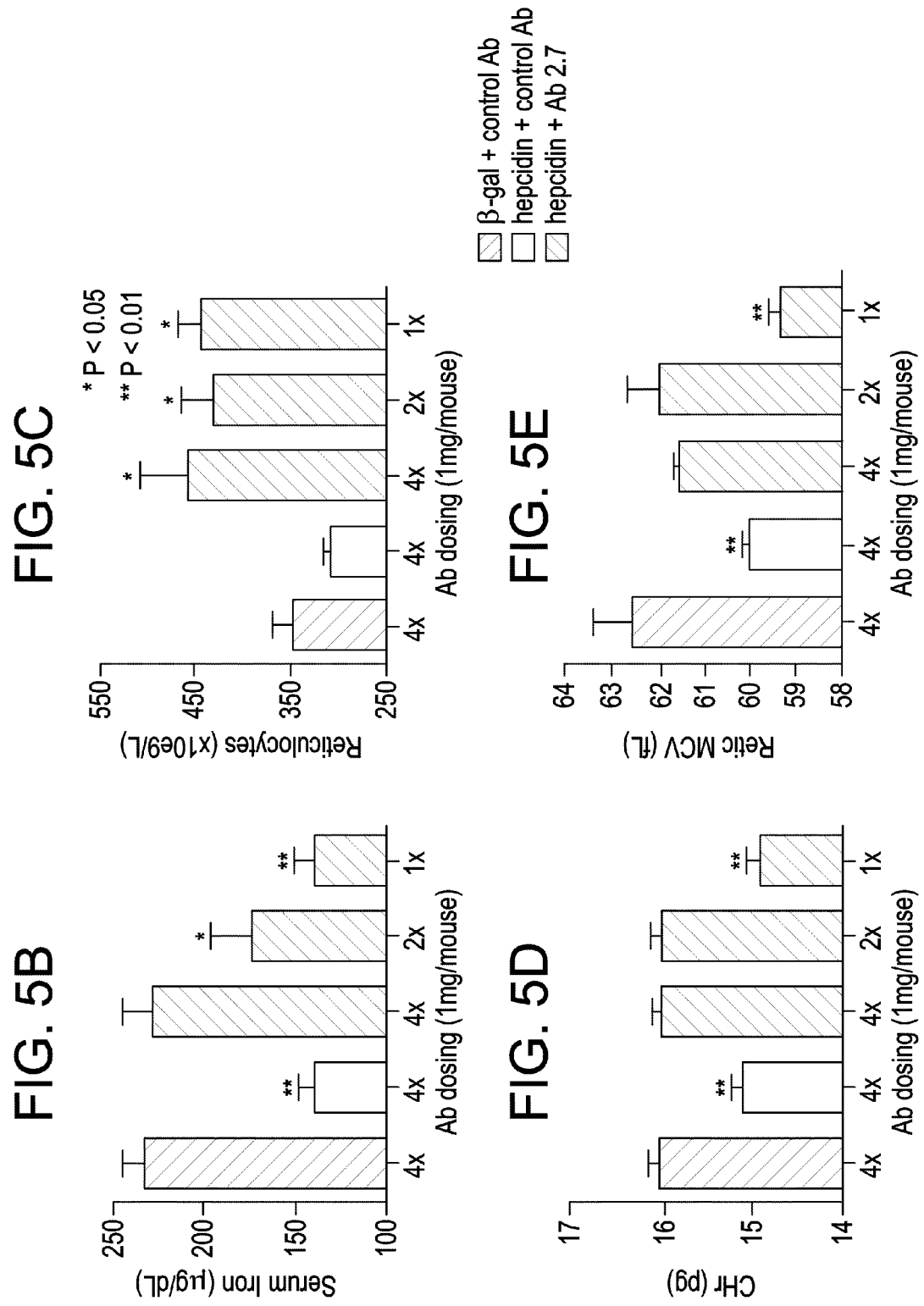


FIG. 5B
Serum Iron (µg/dL)
250
200
150
100
**
*
**
4x
4x
4x
2x
1x
Ab dosing (1mg/mouse)
FIG. 5C
Reticulocytes (x10e9/L)
550
450
350
250
* P < 0.05
** P < 0.01
*
*
*
4x
4x
4x
2x
1x
Ab dosing (1mg/mouse)
β-gal + control Ab
hepcidin + control Ab
hepcidin + Ab 2.7
FIG. 5D
CHr (pg)
17
16
15
14
**
**
4x
4x
4x
2x
1x
Ab dosing (1mg/mouse)
FIG. 5E
Retic MCV (fL)
64
63
62
61
60
59
58
**
**
4x
4x
4x
2x
1x
Ab dosing (1mg/mouse)

FIG. 6A

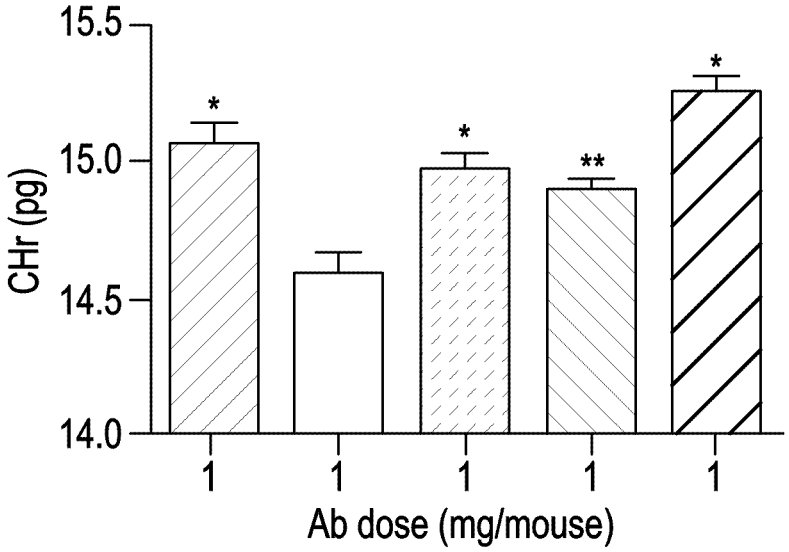
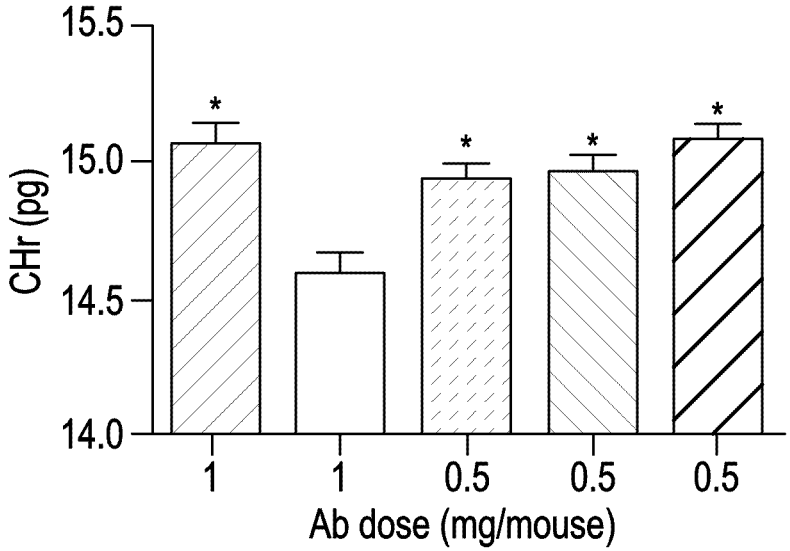

15.5
15.0
14.5
14.0
CHr (pg)
*
*
**
*
1
1
1
1
1
Ab dose (mg/mouse)

FIG. 6B


15.5
15.0
14.5
14.0
CHr (pg)
*
*
*
*
1
1
0.5
0.5
0.5
Ab dose (mg/mouse)

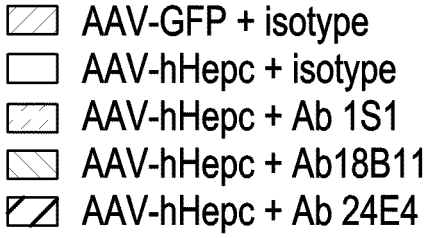

AAV-GFP + isotype
AAV-hHepc + isotype
AAV-hHepc + Ab 1S1
AAV-hHepc + Ab18B11
AAV-hHepc + Ab 24E4

FIG. 7A

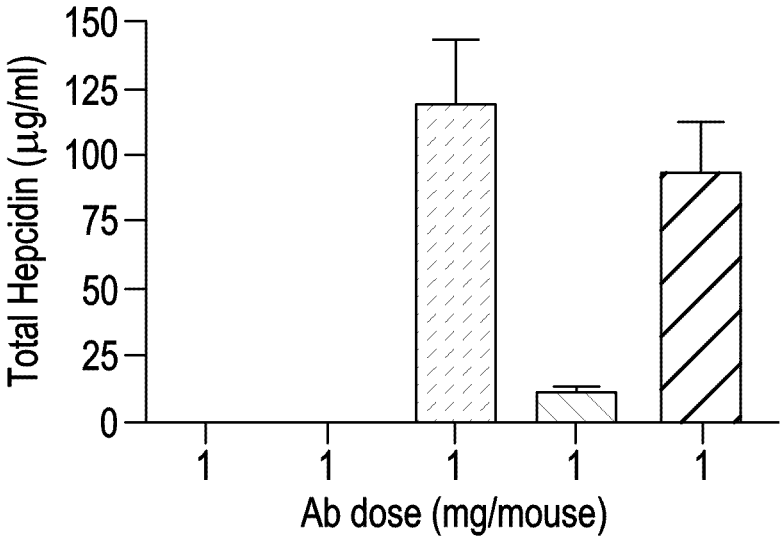

Total Hepcidin (µg/ml)
150
125
100
75
50
25
0
1
1
1
1
1
Ab dose (mg/mouse)

FIG. 7B

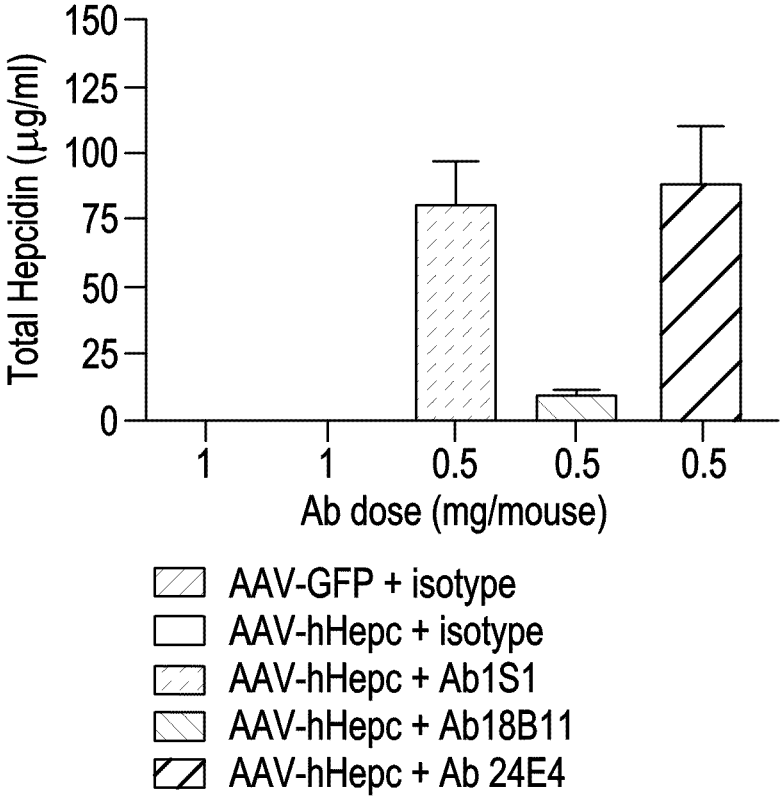

Total Hepcidin (µg/ml)
150
125
100
75
50
25
0
1
1
0.5
0.5
0.5
Ab dose (mg/mouse)
AAV-GFP + isotype
AAV-hHepc + isotype
AAV-hHepc + Ab1S1
AAV-hHepc + Ab18B11
AAV-hHepc + Ab 24E4

FIG. 8

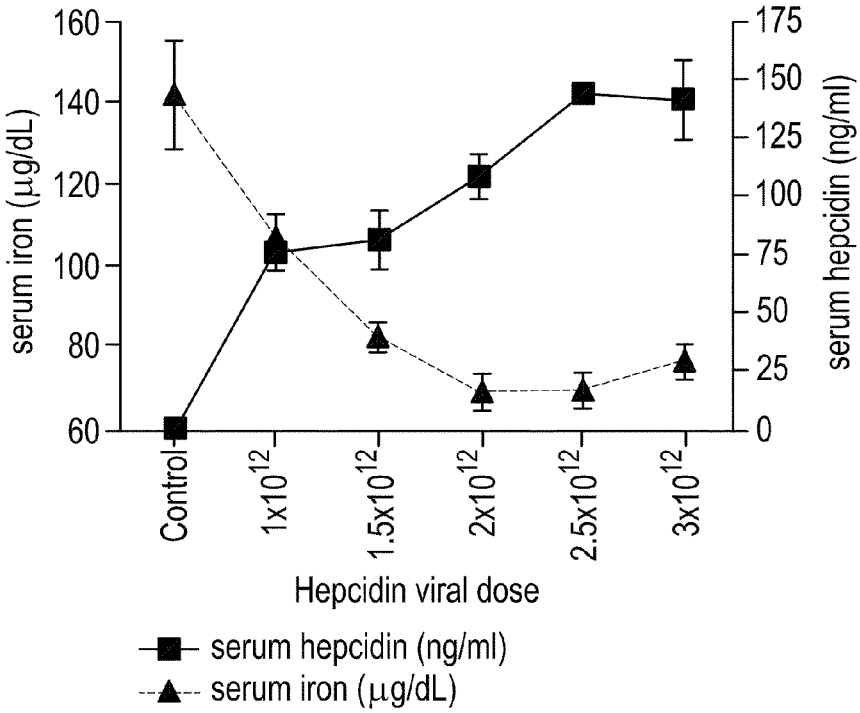

160
140
120
100
80
60
serum iron (µg/dL)
175
150
125
100
75
50
25
0
serum hepcidin (ng/ml)
Control
1x10^12
1.5x10^12
2x10^12
2.5x10^12
3x10^12
Hepcidin viral dose
serum hepcidin (ng/ml)
serum iron (µg/dL)

FIG. 9

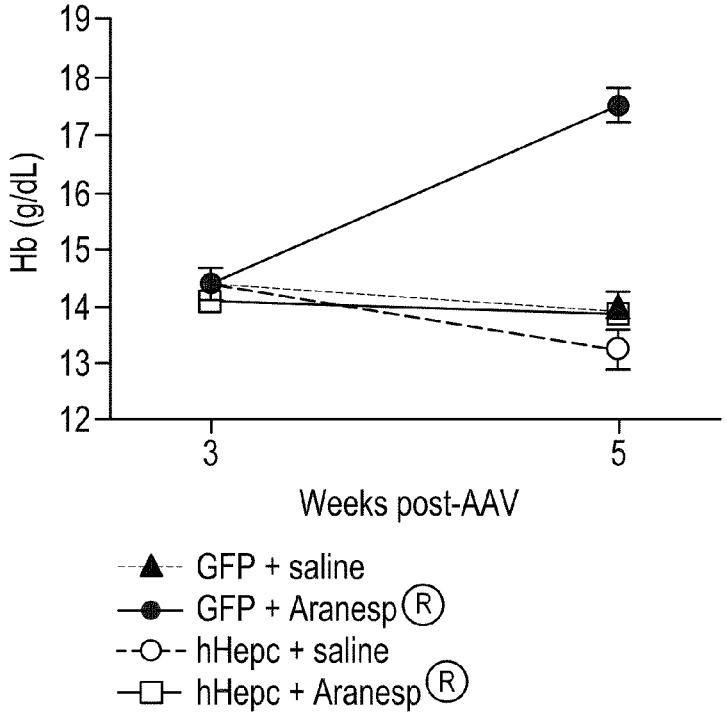

19
18
17
16
15
14
13
12
Hb (g/dL)
3
5
Weeks post-AAV
GFP + saline
GFP + Aranesp®
hHepc + saline
hHepc + Aranesp®

FIG.10A

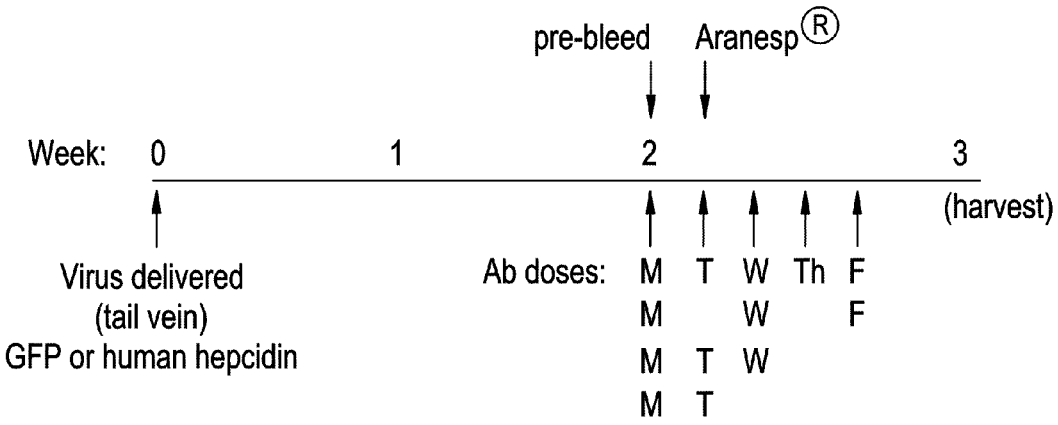

pre-bleed
Aranesp®
Week:
0
1
2
3
(harvest)
Virus delivered
(tail vein)
GFP or human hepcidin
Ab doses:
M T W Th F
M W F
M T W
M T

FIG. 10B

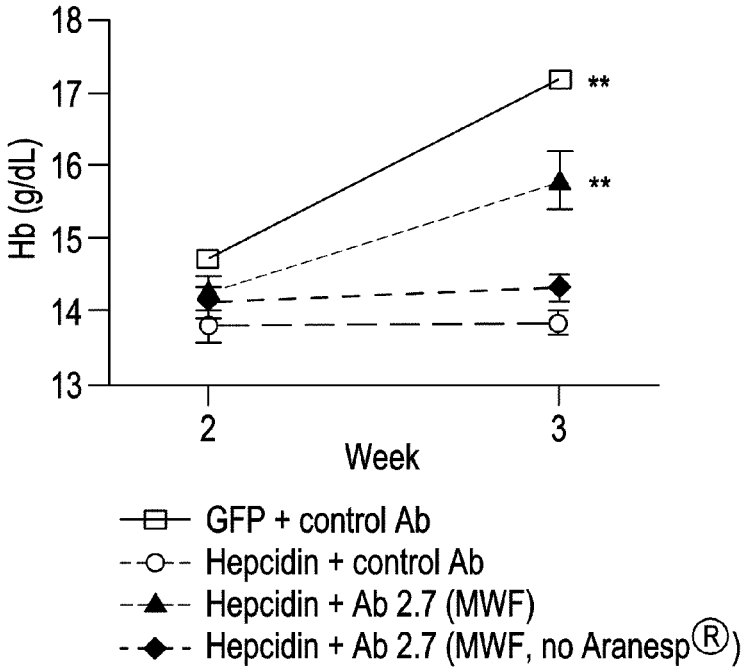


FIG. 10C

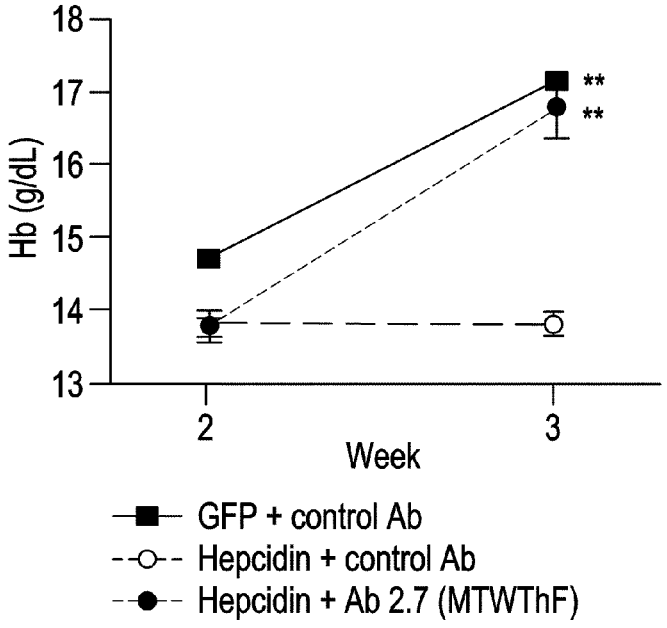


FIG. 10D

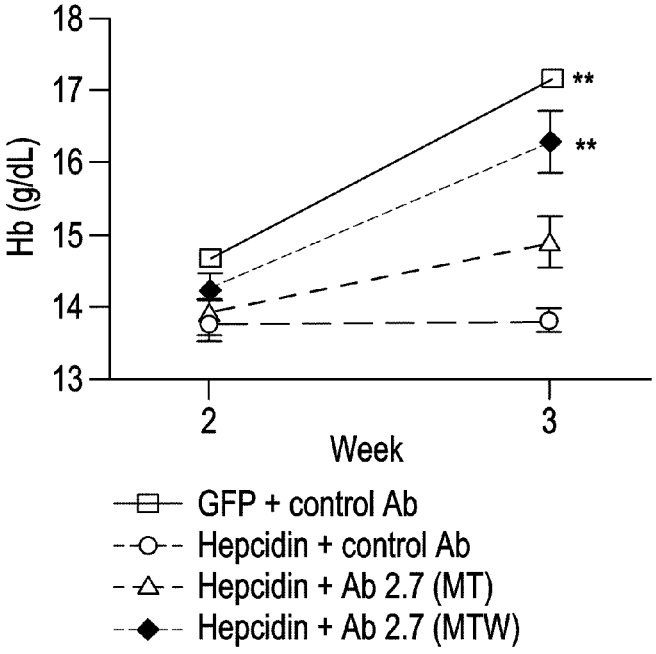


FIG. 10E

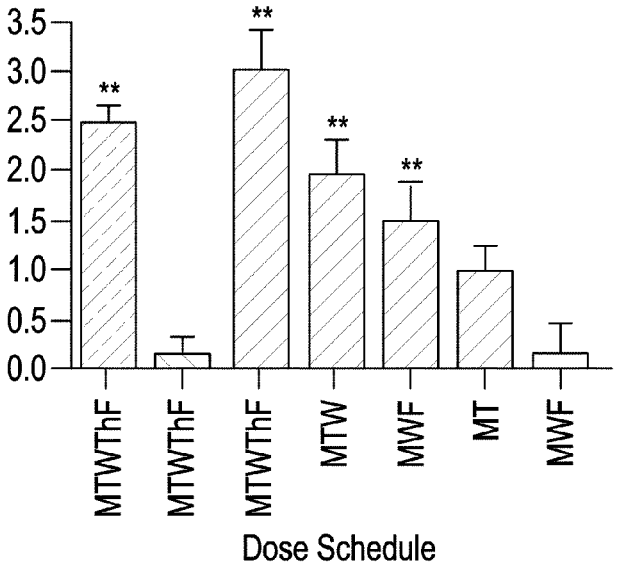


FIG. 11A

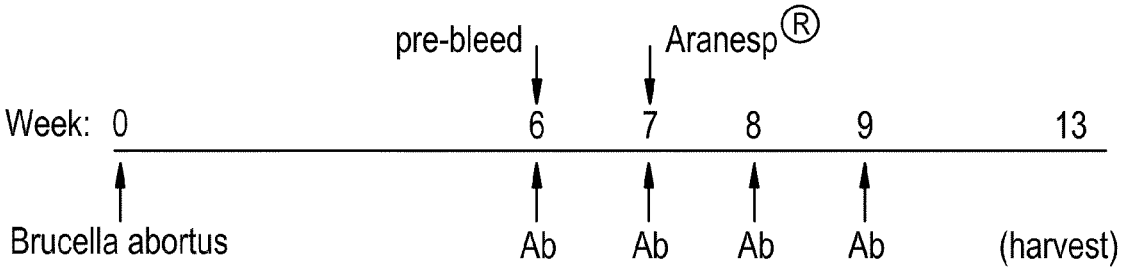


FIG. 11B

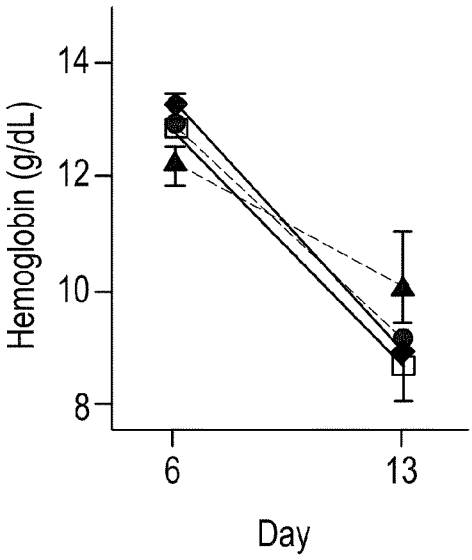
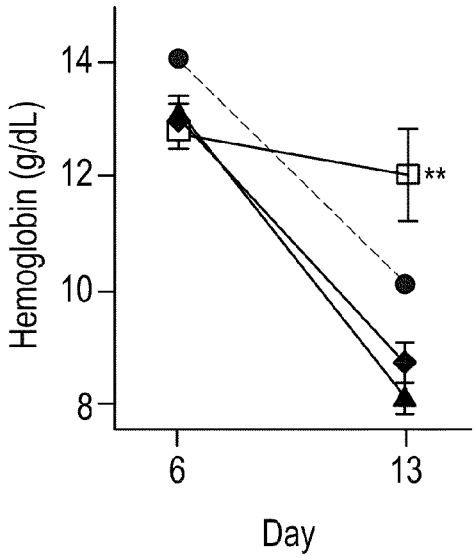


FIG. 11C



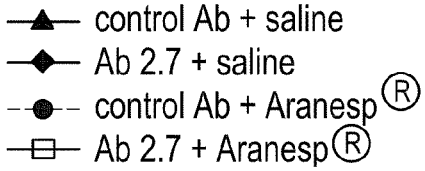


FIG. 12

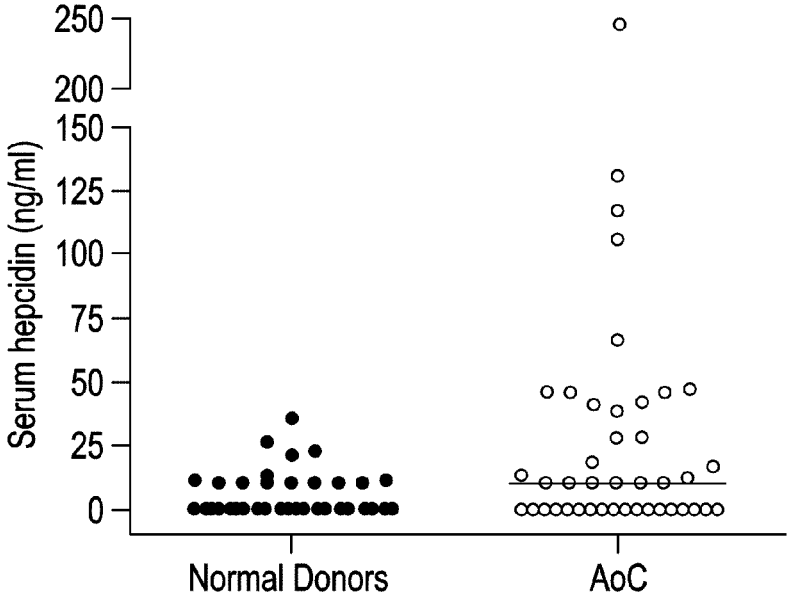

250
200
150
125
100
75
50
25
0
Serum hepcidin (ng/ml)
Normal Donors
AoC

FIG. 13

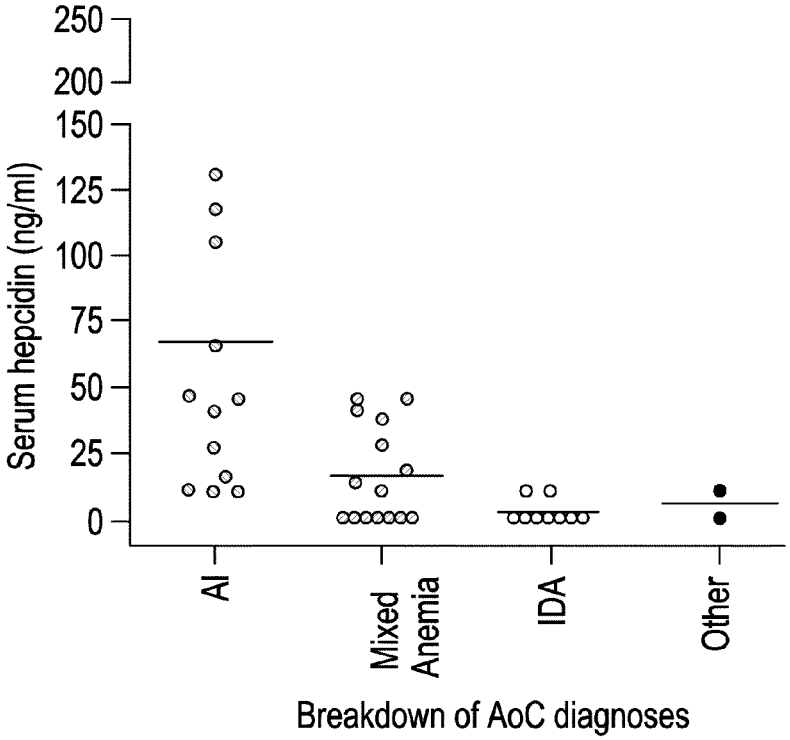

250
200
150
125
100
75
50
25
0
Serum hepcidin (ng/ml)
AI
Mixed Anemia
IDA
Other
Breakdown of AoC diagnoses

FIG. 14A

Current Stratification Scheme

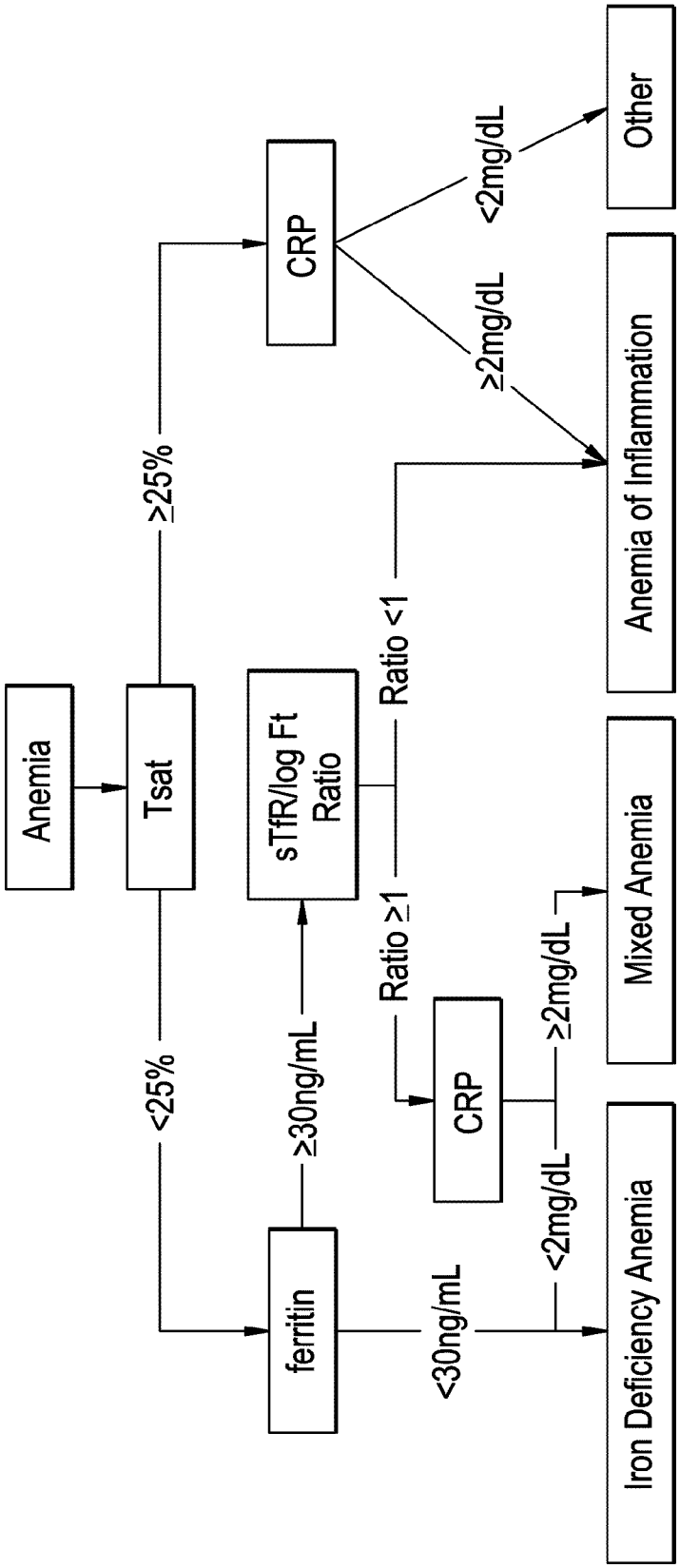


FIG. 14B

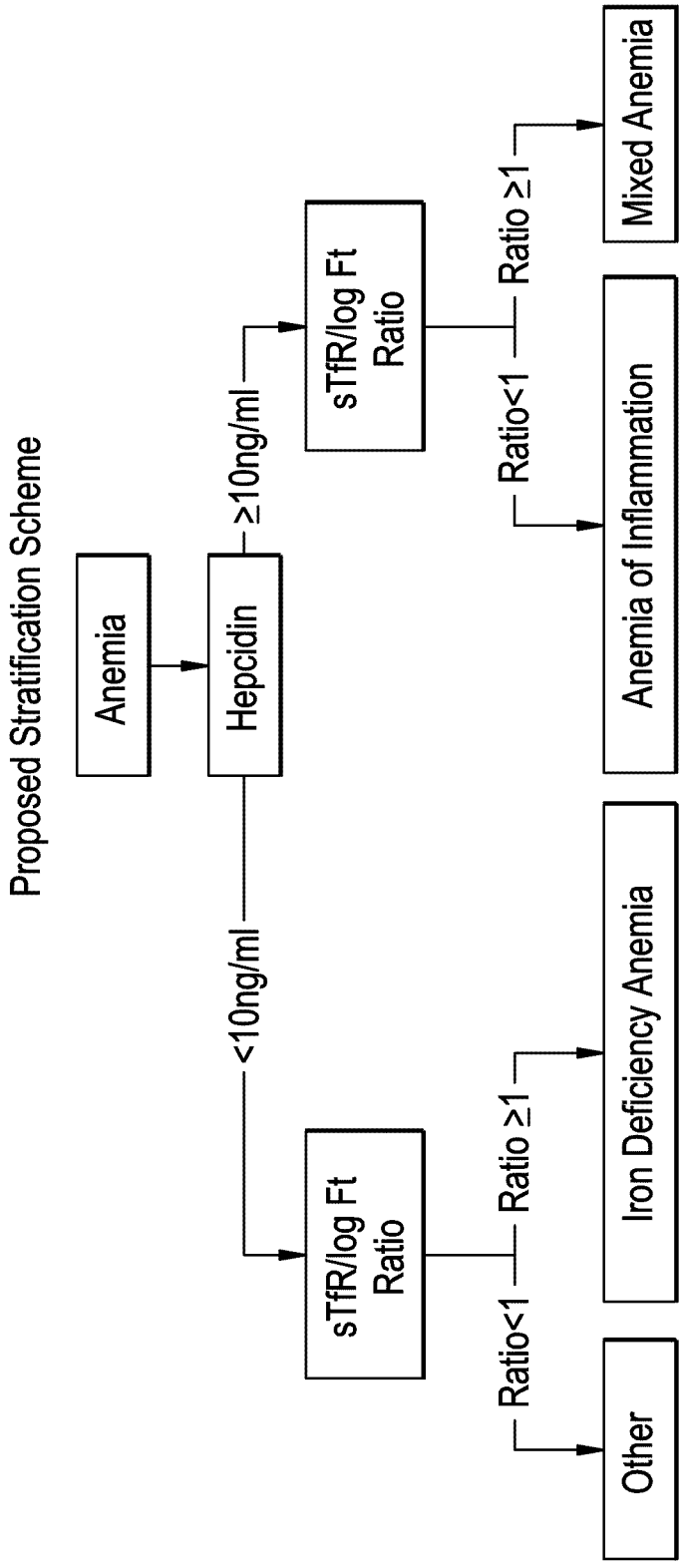

Proposed Stratification Scheme
Anemia
Hepcidin
<10ng/ml
≥10ng/ml
sTfR/log Ft Ratio
Ratio<1
Ratio ≥1
Other
Iron Deficiency Anemia
sTfR/log Ft Ratio
Ratio<1
Ratio ≥1
Anemia of Inflammation
Mixed Anemia

FIG. 15A

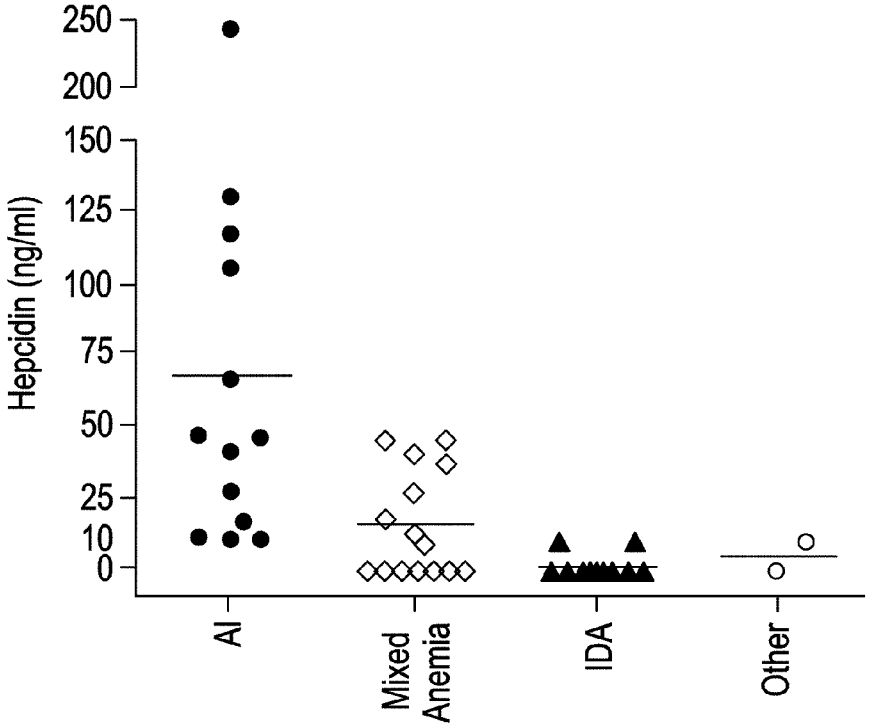


FIG. 15B

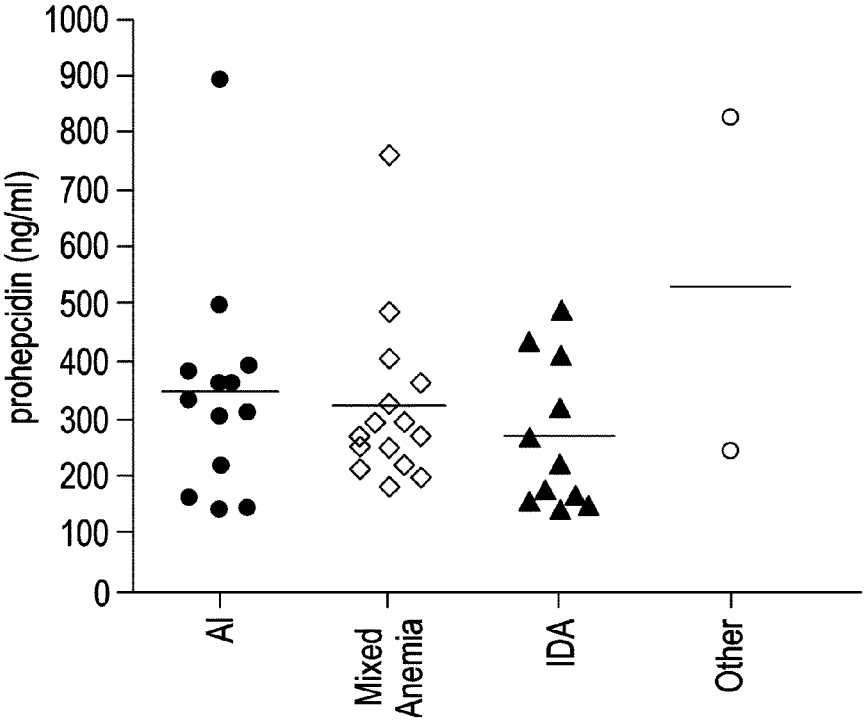


FIG. 16

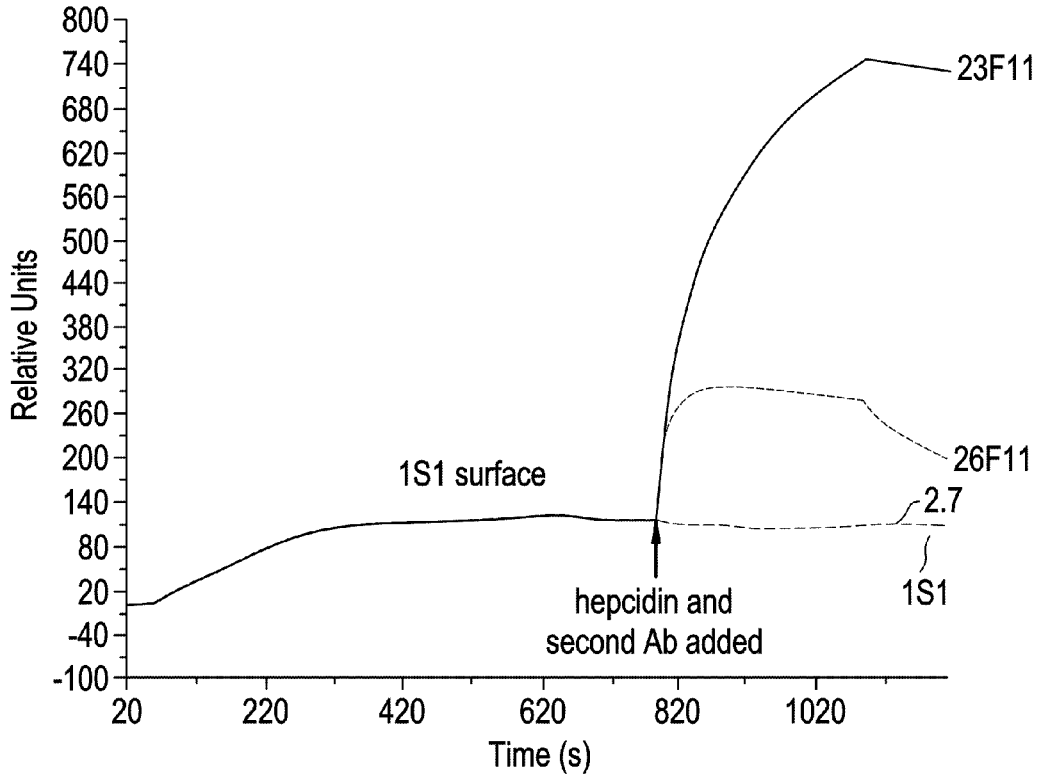

800
740
680
620
560
500
440
380
320
260
200
140
80
20
-40
-100
Relative Units
20
220
420
620
820
1020
Time (s)
23F11
26F11
2.7
1S1
1S1 surface
hepcidin and
second Ab added

FIG. 17

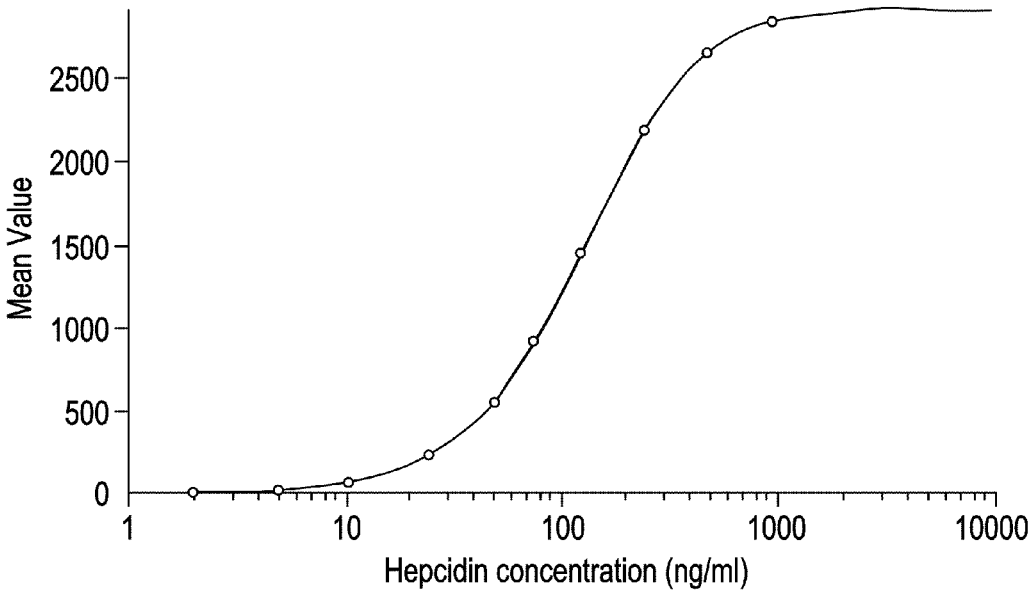

Mean Value
2500
2000
1500
1000
500
0
1
10
100
1000
10000
Hepcidin concentration (ng/ml)

FIG. 18

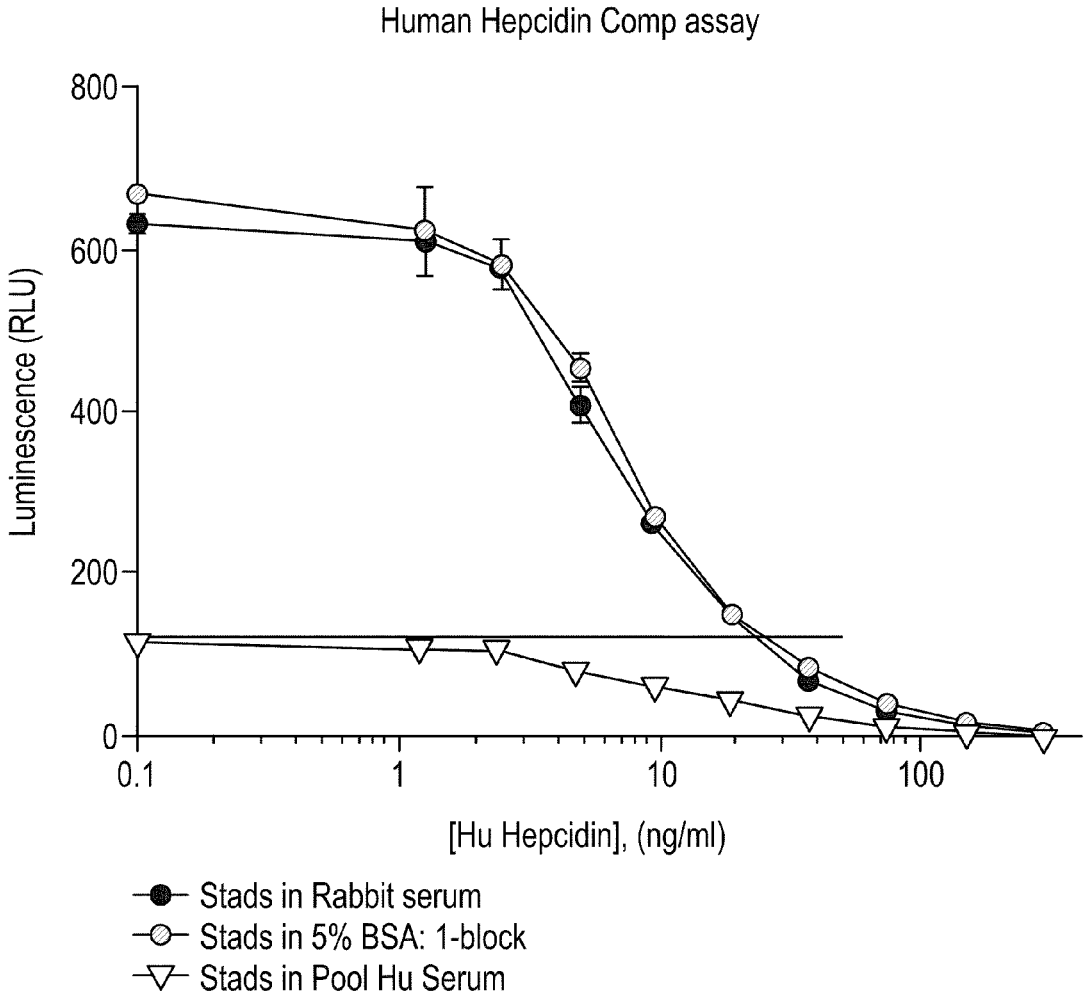

Human Hepcidin Comp assay
800
600
400
200
0
Luminescence (RLU)
0.1
1
10
100
[Hu Hepcidin], (ng/ml)
Stads in Rabbit serum
Stads in 5% BSA: 1-block
Stads in Pool Hu Serum

FIG. 19

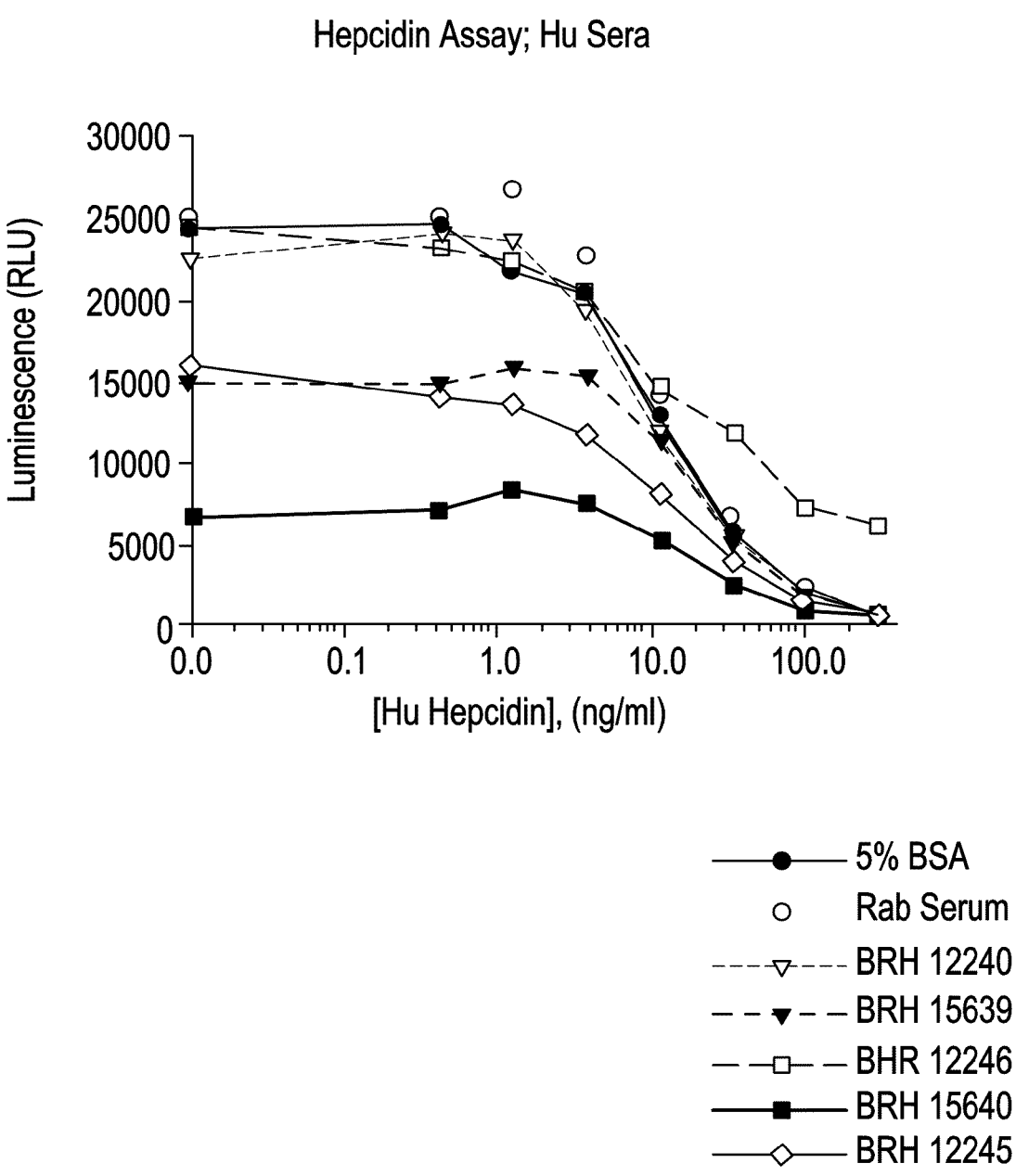

Hepcidin Assay; Hu Sera
Luminescence (RLU)
30000
25000
20000
15000
10000
5000
0
0.0
0.1
1.0
10.0
100.0
[Hu Hepcidin], (ng/ml)
5% BSA
Rab Serum
BRH 12240
BRH 15639
BHR 12246
BRH 15640
BRH 12245

FIG. 20

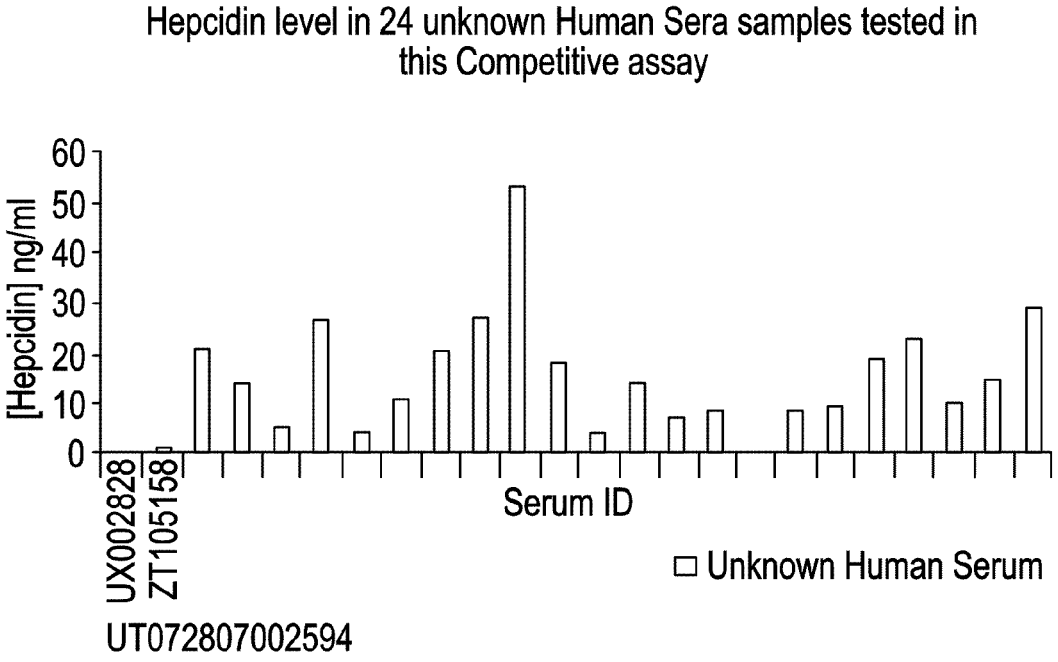

Hepcidin level in 24 unknown Human Sera samples tested in this Competitive assay
[Hepcidin] ng/ml
60
50
40
30
20
10
0
UX002828
ZT105158
UT072807002594
Serum ID
Unknown Human Serum

FIG. 21

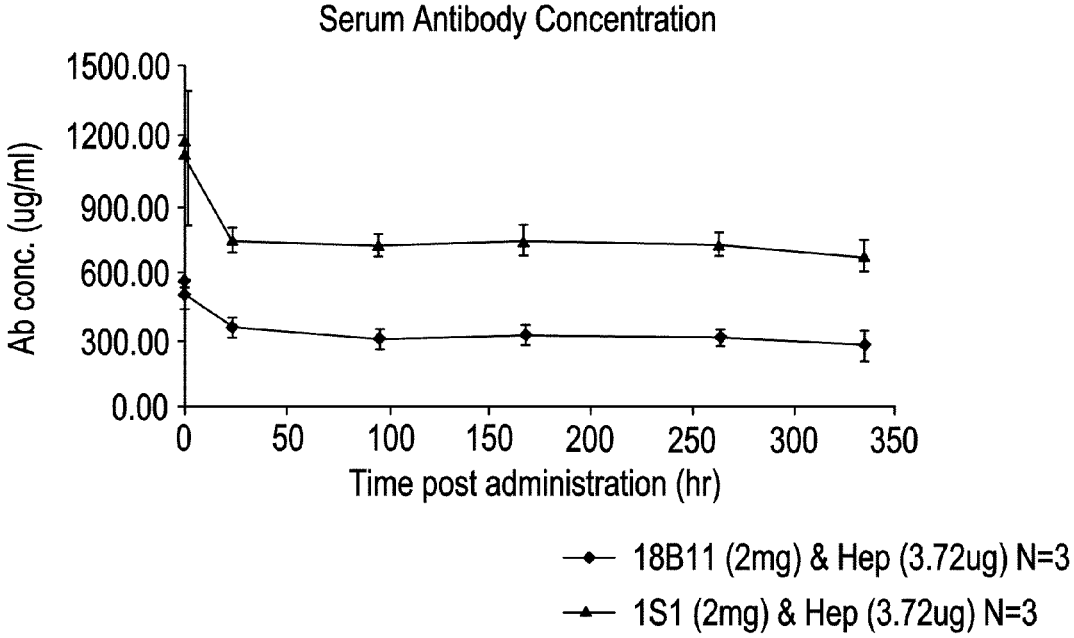

Serum Antibody Concentration
Ab conc. (ug/ml)
1500.00
1200.00
900.00
600.00
300.00
0.00
0
50
100
150
200
250
300
350
Time post administration (hr)
18B11 (2mg) & Hep (3.72ug) N=3
1S1 (2mg) & Hep (3.72ug) N=3

FIG. 22

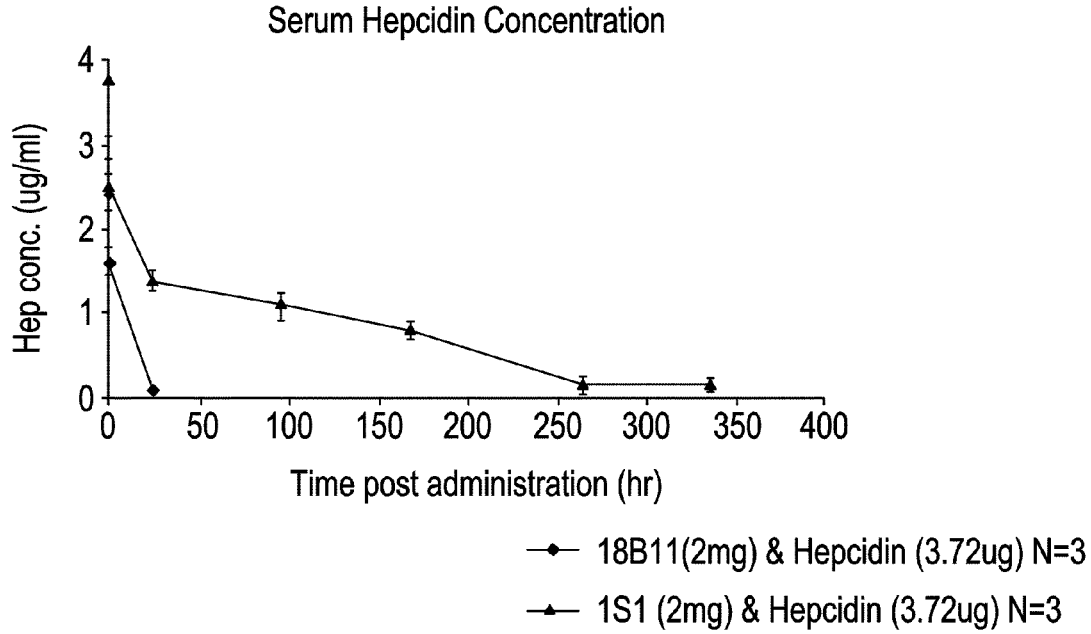

Serum Hepcidin Concentration
Hep conc. (ug/ml)
4
3
2
1
0
0
50
100
150
200
250
300
350
400
Time post administration (hr)
18B11(2mg) & Hepcidin (3.72ug) N=3
1S1 (2mg) & Hepcidin (3.72ug) N=3

FIG. 23

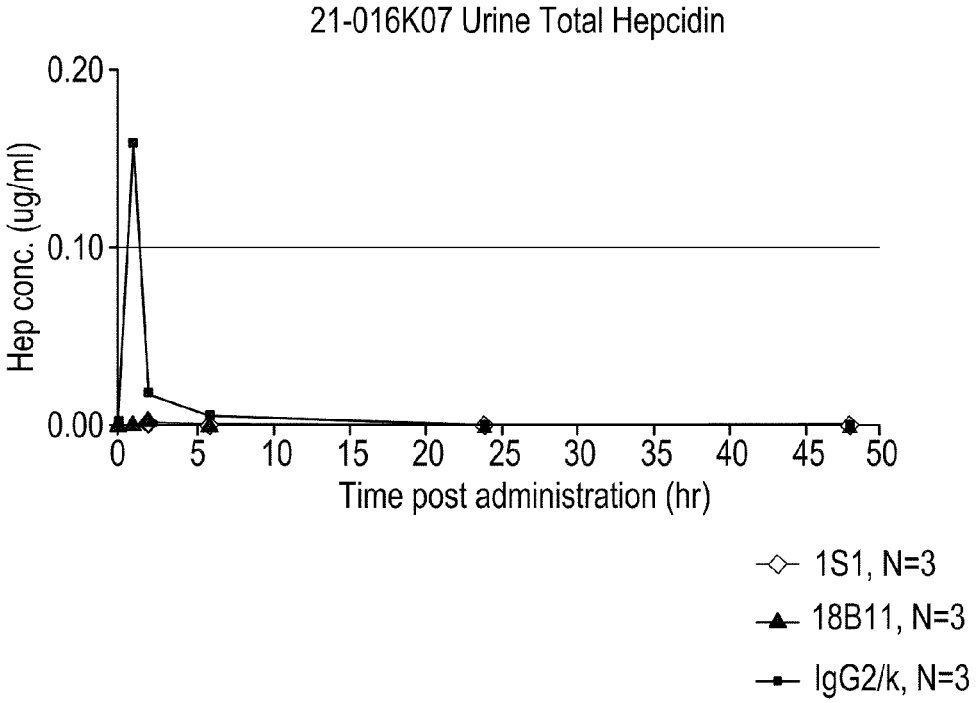

21-016K07 Urine Total Hepcidin
Hep conc. (ug/ml)
0.20
0.10
0.00
0
5
10
15
20
25
30
35
40
45
50
Time post administration (hr)
1S1, N=3
18B11, N=3
IgG2/k, N=3

FIG. 24

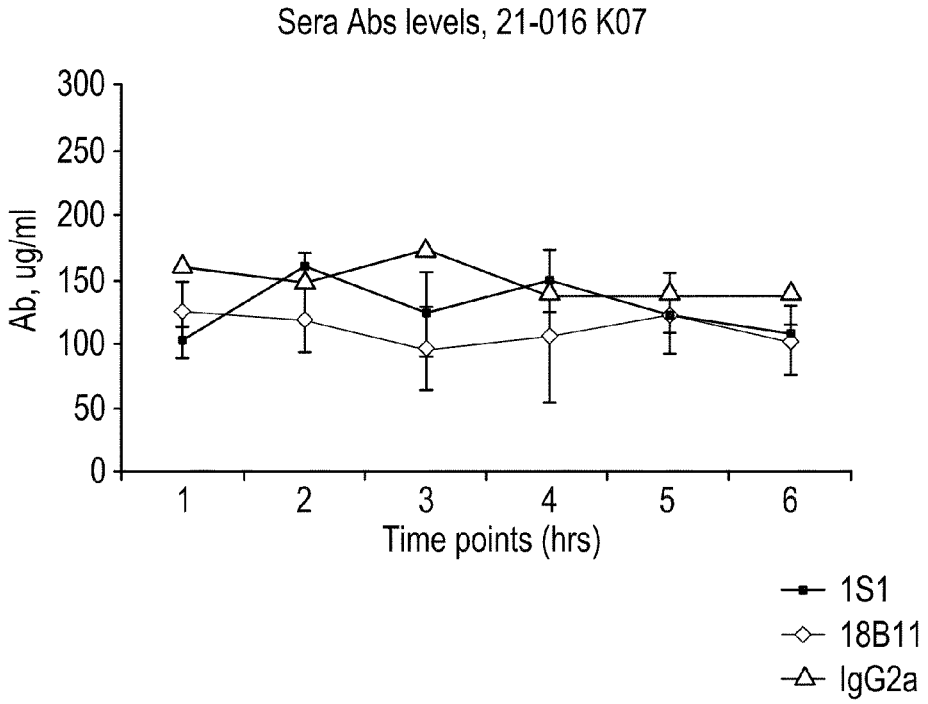

Sera Abs levels, 21-016 K07
Ab, ug/ml
300
250
200
150
100
50
0
1
2
3
4
5
6
Time points (hrs)
1S1
18B11
IgG2a

FIG. 25

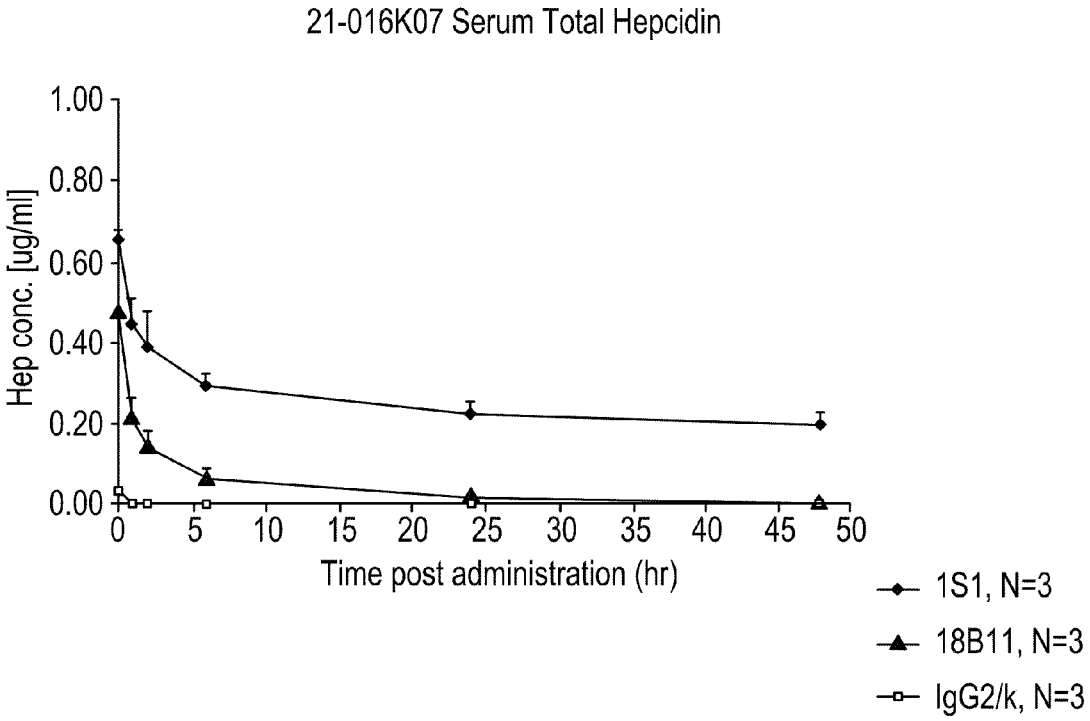
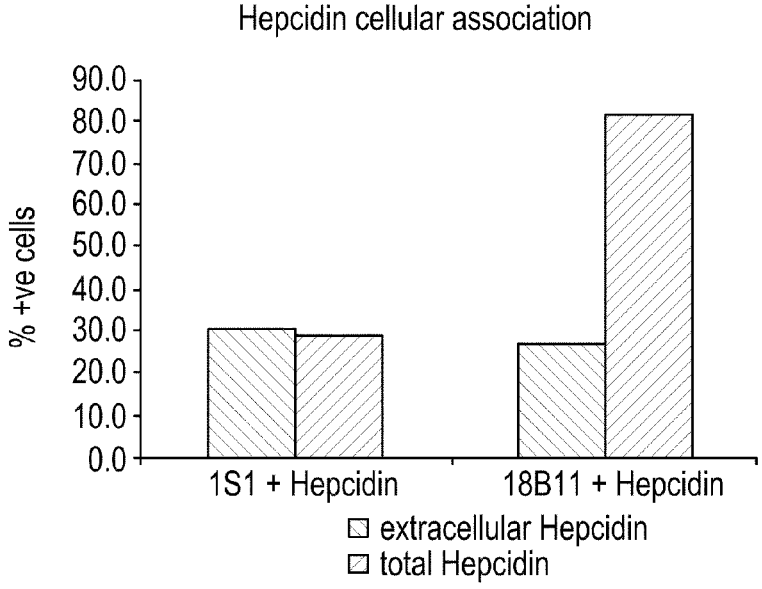

21-016K07 Serum Total Hepcidin
Hep conc. [ug/ml]
1.00
0.80
0.60
0.40
0.20
0.00
0
5
10
15
20
25
30
35
40
45
50
Time post administration (hr)
1S1, N=3
18B11, N=3
IgG2/k, N=3

FIG. 26


Hepcidin cellular association
% +ve cells
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
1S1 + Hepcidin
18B11 + Hepcidin
extracellular Hepcidin
total Hepcidin

ANTI-HEPCIDIN ANTIBODIES AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national stage application under 35 U.S.C. 371 of International Application No. PCT/US2009/002606, having an international filing date of 28 Apr. 2009, which claims the benefit of U.S. Provisional Application No. 61/049,687, filed 01 May 2008, which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic ASCII ".txt" format. The Sequence Listing is provided as a file entitled "A-1419-US-PCT_SeqList.txt" and was created on 28 Apr. 2009. The text file is 295,945 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to hepcidin, hepcidin antagonists (including antibodies that bind hepcidin) and their ability to modulate hepcidin activity.

BACKGROUND OF THE INVENTION

Iron is an essential trace element required for growth and development of all living organisms. Iron content in mammals is regulated by controlling iron absorption, iron recycling, and release of iron from the cells in which it is stored. Iron is absorbed predominantly in the duodenum and upper jejunum by enterocytes. A feedback mechanism exists that enhances iron absorption in individuals who are iron deficient, and that reduces iron absorption in individuals with iron overload (Andrews, *Ann. Rev. Genomics Hum. Genet.,* 1:75 (2000); Philpott, *Hepatology,* 35:993 (2002); Beutler et al., *Drug-Metab. Dispos.,* 29:495 (2001)). Iron is recycled from degraded red cells by reticuloendothelial macrophages in bone marrow, hepatic Kupffer cells and spleen. Iron release is controlled by ferroportin, a major iron export protein located on the cell surface of enterocytes, macrophages and hepatocytes, the main cells capable of releasing iron into plasma. Hepcidin binds to ferroportin and decreases its functional activity by causing it to be internalized from the cell surface and degraded. (Nemeth et al., *Science,* 306:2090-3, 2004; De Domenico et al., *Mol. Biol. Cell.,* 18:2569-2578, 2007).

Hepcidin is an important regulator of iron homeostasis (Philpott, Hepatology, 35:993 (2002); Nicolas et al., *Proc. Natl. Acad. Sci. USA,* 99:4396 (2002)). High levels of human hepcidin result in reduced iron levels, and vice versa. Mutations in the hepcidin gene which result in lack of hepcidin activity are associated with juvenile hemochromatosis, a severe iron overload disease (Roetto et al., *Nat. Genet.,* 33:21-22, 2003). Studies in mice have demonstrated a role of hepcidin in control of normal iron homeostasis (Nicolas et al., *Nat. Genet.,* 34:97-101, 2003; Nicolas et al., *Proc. Natl. Acad. Sci. USA,* 99:4596-4601, 2002; Nicolas et al., *Proc. Natl. Acad. Sci. USA,* 98:8780-8785, 2001.).

In addition, data is accumulating implicating hepcidin in iron sequestration during inflammation (See, e.g., Weinstein et al., *Blood,* 100:3776-36781, 2002; Kemna et al., *Blood,* 106:1864-1866, 2005; Nicolas et al., *J. Clin. Invest.,* 110:1037-1044, 2002; Nemeth et al., *J. Clin. Invest.,* 113:1271-1276, 2004; Nemeth et al., *Blood,* 101:2461-2463, 2003 and Rivera et al., *Blood,* 105:1797-1802, 2005). Hepcidin gene expression has been observed to be robustly upregulated after inflammatory stimuli, such as infections, which induce the acute phase response of the innate immune systems of vertebrates. In mice, hepcidin gene expression was shown to be upregulated by lipopolysaccharide (LPS), turpentine, Freund's complete adjuvant, and adenoviral infections. Hepcidin expression is induced by the inflammatory cytokine interleukin-6 (IL-6). A strong correlation between hepcidin expression and anemia of inflammation was also found in patients with chronic inflammatory diseases, including bacterial, fungal, and viral infections.

Human hepcidin, a 25 amino acid peptide with anti-microbial and iron-regulating activity, was discovered independently by two groups investigating novel anti-microbial peptides. (Krause et al., *FEBS Lett.,* 480:147 (2000); Park et al., *J. Biol. Chem.,* 276:7806 (2001)). It has also been referred to as LEAP-1 (liver-expressed antimicrobial peptide). A hepcidin cDNA encoding an 83 amino acid pre-propeptide in mice and an 84 amino acid pre-propeptide in rat and human were subsequently identified in a search for liver specific genes that were regulated by iron (Pigeon et al., *J. Biol. Chem.,* 276:7811 (2001)). The 24 residue N-terminal signal peptide is first cleaved to produce pro-hepcidin, which is then further processed to produce mature hepcidin, found in both blood and urine. In human urine, the predominant form contains 25 amino acids, although shorter 22 and 20 amino acid peptides are also present.

The mature peptide is notable for containing eight cysteine residues linked as four disulfide bridges. The structure of hepcidin was studied by Hunter et al., *J. Biol. Chem.,* 277:37597-37603 (2002), by NMR using chemically synthesized hepcidin with an identical HPLC retention time to that of native hepcidin purified from urine. Hunter et al. reported their determination that hepcidin folded into a hairpin loop structure containing a vicinal disulfide bond (C1-C8, C2-C7, C3-C6, C4-C5). See also Lauth et al., *J. Biol. Chem.,* 280:9272-9282 (2005). However, as discovered and disclosed in copending U.S. patent application Ser. No. 12/022,515, incorporated by reference herein in its entirety, the structure of hepcidin was determined to have a disulfide bond connectivity different than noted above.

U.S. Patent Application Publication Nos. 2003/0187228, 2004/0096987, 2004/0096990, 2005/0148025, 2006/0019339, 2005/0037971 and 2007/0224186; U.S. Pat. Nos. 7,232,892 and 7,294,690 and International Publication No. WO 02/98444 discuss hepcidin antibodies.

SUMMARY OF THE INVENTION

Various embodiments of the invention provide antibodies, including monoclonal antibodies that specifically bind human hepcidin, methods of producing such antibodies, methods of using such antibodies for detecting hepcidin, pharmaceutical formulations including such antibodies, methods of preparing the pharmaceutical formulations, and methods of treating patients with the pharmaceutical formulations, including combination therapy with erythropoiesis stimulators as described below. Nucleic acids encoding such antibodies, vectors and recombinant host cells comprising such nucleic acids, and methods of producing such antibodies are also provided.

In some embodiments, an isolated antibody is provided that binds to human hepcidin of SEQ ID NO: 9 with an affinity K_D of less than about 10^{-8}M that exhibits at least one of the

properties selected from the group consisting of: (a) at least about a 50-fold higher K_D at a pH of about 5.5 or about 6 compared to its K_D for said hepcidin at a pH of about 7.4; (b) at least about a 5-fold faster clearance of said hepcidin compared to antibody 1S1; and (c) an off rate of about 6×10^{-2} s^{-1} or higher at about pH 5.5 or about pH 6. Alternatively, or in addition to one or more of the foregoing properties, the antibody exhibits at least one of the properties selected from the group consisting of: (a) reduces the level of total human hepcidin in serum by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% in a C57BL/6 mouse about 24 hours after the administration to said mouse of (i) a 1 mg doses of said antibody and (ii) a pre-complexed single dose of 3.7 μg of human hepcidin with a 1 mg dose of said antibody; (b) reduces the level of total human hepcidin in serum in a mouse by at least about 20%, 30%, 40%, 50%, 60%, 70%, 80% or 90% about 24 hours after said mouse is administered a single dose of 3.7 μg of human hepcidin, wherein said hepcidin is administered three days after said mouse is pre-dosed with said antibody; (c) results in a greater than about 50% reduction in overall accumulation of total serum hepcidin in mice treated with said antibody compared to antibody 1S1; and (d) results in at least about a 2-fold higher intracellular accumulation of hepcidin in FcRn transfected HEK293 cells incubated with said antibody compared to antibody 1S1.

In some embodiments, an isolated antibody is provided that binds to human hepcidin of SEQ ID NO: 9 with an affinity K_D of less than about 10^{-8}M, wherein said antibody increases circulating iron level or Tsat in a mouse overexpressing human hepcidin for at least 1 day, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11 days or more after a single dose of antibody.

In some embodiments, an isolated antibody is provided that binds to human hepcidin of SEQ ID NO: 9, with an affinity K_D of at least 10^{-8}M, wherein said antibody is obtained by: (a) replacing an amino acid in the heavy or light chain of said antibody with a histidine; (b) screening the antibody obtained in (a) for differential pH binding; (c) replacing another amino acid in the heavy or light chain of said antibody with a histidine; and (d) screening said antibody for having at least one of the properties selected from the group consisting of: (i) at least about 50-1000 fold higher K_D at about pH 5.5 or about pH 6 compared to its K_D for said hepcidin at about pH 7.4; and (ii) an off rate of about 6×10^{-2} s^{-1} or higher at about pH 5.5 or about pH 6.

In some embodiments, an antibody described herein decreases iron in ferroportin expressing cells stimulated with 50 ng/mL hepcidin at an EC_{50} of about 20 nM or less; and/or increases the level in a subject of one of at least hemoglobin or hematocrit, or both; and/or increases in a subject one of at least the red blood cell count, the red blood cell hemoglobin content or the red blood cell mean cell volume of red blood cell count, or any combinations thereof; and/or increases in a subject one of at least the reticulocyte count, the reticulocyte hemoglobin content or the reticulocyte mean cell volume of reticulocyte count, or any combinations thereof; and/or inhibits the iron-regulating activity of hepcidin.

In some embodiments, the antibody comprises an amino acid sequence at least 90% identical to SEQ ID NO: 170 or to SEQ ID NO: 168, said polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 171-176, and any sequences comprising at least one amino acid change to any of SEQ ID NOs: 171-176. In one aspect, the antibody comprises SEQ ID NOs: 171-173. In another aspect, the antibody comprises SEQ ID NOs: 174-176.

In some embodiments, an antibody described herein comprises an amino acid sequence at least 90% identical to SEQ ID NO: 333 or to SEQ ID NO: 331, said polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 334-349, and any sequences comprising at least one amino acid change to any of SEQ ID NOs: 334-349. In one aspect, an antibody described herein comprises SEQ ID NOs: 334-346. In another aspect, an antibody described herein comprises SEQ ID NOs: 347-349.

In some embodiments, an antibody described herein comprises an amino acid sequence at least 90% identical to SEQ ID NO: 343 or to SEQ ID NO: 341, said polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 344-349, and any sequences comprising at least one amino acid change to any of SEQ ID NOs: 344-349. In one aspect, an antibody described herein comprises SEQ ID NOs: 344-346. In another aspect, an antibody described herein comprises SEQ ID NOs: 347-349.

In some embodiments, an antibody described herein comprises an amino acid sequence at least 90% identical to SEQ ID NO: 353 or to SEQ ID NO: 351, said polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 354-359, and any sequences comprising at least one amino acid change to any of SEQ ID NOs: 354-359. In one aspect, an antibody described herein comprises SEQ ID NOs: 354-356. In another aspect, an antibody described herein comprises SEQ ID NOs: 357-359.

In some embodiments, an antibody described herein comprises an amino acid sequence at least 90% identical to SEQ ID NO: 363 or to SEQ ID NO: 361, said polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 364-369, and any sequences comprising at least one amino acid change to any of SEQ ID NOs: 364-369. In one aspect, an antibody described herein comprises SEQ ID NOs: 364-366. In another aspect, an antibody described herein comprises SEQ ID NOs: 367-369.

In some embodiments, an antibody described herein comprises an amino acid sequence at least 90% identical to SEQ ID NO: 373 or to SEQ ID NO: 37, said polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 374-379, and any sequences comprising at least one amino acid change to any of SEQ ID NOs: 374-379. In one aspect, an antibody described here comprises SEQ ID NOs: 374-376. In another aspect, an antibody described herein comprises SEQ ID NOs: 377-379.

In some embodiments, an antibody described herein comprises an amino acid sequence at least 90% identical to SEQ ID NO: 383 or to SEQ ID NO: 381, said polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 384-389, and any sequences comprising at least one amino acid change to any of SEQ ID NOs: 384-389. In one aspect, an antibody described herein comprises SEQ ID NOs: 384-386. In another aspect, an antibody described herein comprises comprising SEQ ID NOs: 387-389.

In some embodiments, an antibody described herein comprises an amino acid sequence at least 90% identical to SEQ ID NO: 393 or to SEQ ID NO: 391, said polypeptide comprising at least one amino acid sequence selected from the group consisting of SEQ ID NOs: 394-399, and any sequences comprising at least one amino acid change to any of SEQ ID NOs: 394-399. In one aspect, an antibody described herein comprises SEQ ID NOs: 394-396. In

another aspect, an antibody described herein comprises comprising SEQ ID NOs: 397-399.

In some embodiments, an antibody described here comprises an amino acid sequence of SEQ ID NO: 170 wherein at least one, two, three or all four of the amino acids at positions 52, 57, 99 and 107 of said amino acid sequence are replaced with a histidine. Such an antibody may further comprise SEQ ID NO: 168. In other embodiments, the antibody comprises an amino acid sequence of SEQ ID NO: 168 wherein at least one or both of the amino acids at positions 27 and 89 of said amino acid sequence are replaced with a histidine. Such an antibody may further comprise SEQ ID NO: 170. Optionally, any of the foregoing modified SEQ ID NO: 170 and any of the foregoing modified SEQ ID NO: 168 may be combined in an antibody. In one embodiment, the amino acids at positions 57 and 107 of SEQ ID NO: 170 are both replaced with a histidine. In another embodiment, the amino acid at position 107 of SEQ ID NO: 170 and the amino acid at position 27 of SEQ ID NO: 168 are both replaced with a histidine. In another embodiment, the amino acid at position 107 of SEQ ID NO: 170 and the amino acid at position 89 of SEQ ID NO: 168 are both replaced with a histidine. In yet another embodiment, the amino acids at positions 99 and 107 of SEQ ID NO: 170 are both replaced with a histidine.

Any of the foregoing antibodies may be a monoclonal antibody, or a chimeric, humanized, or human antibody. In some embodiments, the antibody is an IgG isotype, such as an IgG1, IgG2, IgG3 or IgG4 isotype.

In another aspect, embodiments of the invention include an isolated nucleic acid molecule comprising a nucleotide sequence that encodes any of the foregoing antibodies, an expression vector comprising any of the isolated nucleic acid molecules, operably linked to a regulatory control sequence, host cells comprising such isolated nucleic acid molecules or vectors, and methods of using such host cells to produce an antibody. Such production methods comprise culturing the host cell under suitable conditions such that the nucleic acid is expressed to produce the antibody, and optionally recovering the antibody from the host cell or culture medium. In a related embodiment, an isolated antibody or agent produced by the aforementioned method is provided.

Embodiments described herein include a composition that contains any of the foregoing antibodies, e.g. in a therapeutically effective amount, and a pharmaceutically acceptable carrier, diluent or excipient. In a related aspect, embodiments of the invention include a method of treating a disorder of iron homeostasis in a subject in need thereof by administering any of the foregoing antibodies or compositions, e.g., in a therapeutically effective amount. Exemplary disorders of iron homeostasis include anemia, sepsis, anemia of inflammation, anemia of cancer, chemotherapy induced anemia, chronic inflammatory anemia, congestive heart failure, end stage renal disorder, chronic kidney disease (stage I, II, III, IV or V), iron deficiency anemia, a disorder of iron homeostasis, ferroportin disease, hemochromatosis, diabetes, inflammation, rheumatoid arthritis, arteriosclerosis, tumors, vasculitis, systemic lupus erythematosus, hemoglobinopathies, and red blood cell disorders. In related aspects, embodiments of the invention provide methods of treating a human with an elevated level of hepcidin, or methods of treating a human with anemia, by administering any of the foregoing antibodies or compositions, e.g. in a therapeutically effective amount. Also provided are uses of any of the foregoing antibodies in preparation of a medicament for treating any of the foregoing subjects or conditions.

It is understood that co-administration methods involving administration of antibodies with a second therapeutic agent, as described herein, encompass not only the use of the antibody in preparation of a medicament for co-administration with the second therapeutic agent, but also the use of the second therapeutic agent in preparation of a medicament for co-administration with the antibody.

In some embodiments, the mammal is a human suffering from a condition selected from the group consisting of African iron overload, alpha thalassemia, Alzheimer's disease, anemia, anemia of cancer, anemia of chronic disease, anemia of inflammation, arteriosclerosis or atherosclerosis (including coronary artery disease, cerebrovascular disease or peripheral occlusive arterial disease), ataxias, ataxias related to iron, atransferrinemia, cancer, ceruloplasmin deficiency, chemotherapy-induced anemia, chronic renal/kidney disease (stage I, II, III, IV or V), including end stage renal disease or chronic renal/kidney failure, cirrhosis of liver, classic hemochromatosis, collagen-induced arthritis (CIA), conditions with hepcidin excess (elevated hepcidin), congenital dyserythropoietic anemia, congestive heart failure, Crohn's disease, diabetes, disorders of iron biodistribution, disorders of iron homeostasis, disorders of iron metabolism, ferroportin disease, ferroportin mutation hemochromatosis, folate deficiency, Friedrich's ataxia, funicular myelosis, gracile syndrome, *H. pyelori* infection or other bacterial infections, Hallervordan Spatz disease, hemochromatosis, hemochromatosis resulting from mutations in transferrin receptor 2, hemoglobinopathies, hepatitis, hepatitis (Brock), hepatitis C, hepatocellular carcinoma, hereditary hemochromatosis, HIV or other viral illnesses, Huntington's disease, hyperterritinemia, hypochromic microcytic anemia, hypoferremia, insulin resistance, iron deficiency anemia, iron deficiency disorders, iron overload disorders, iron-deficiency conditions with hepcidin excess, juvenile hemochromatosis (HFE2), multiple sclerosis, mutation in transferrin receptor 2, HFE, hemojuvelin, ferroportin or other genes of iron metabolism, neonatal hemochromatosis, neurodegenerative diseases related to iron, osteopenia, osteoporosis pancreatitis, Pantothenate kinase-associated neurodegeneration, Parkinson's disease, pellagra, pica, porphyria, porphyria cutanea tarda, pseudoencephalitis, pulmonary hemosiderosis, red blood cell disorders, rheumatoid arthritis, sepsis, sideroblastic anemia, systemic lupus erythematosus, thalassemia, thalassemia intermedia, transfusional iron overload, tumors, vasculitis, vitamin B6 deficiency, vitamin B12 deficiency, and/or Wilson's disease.

In some embodiments, methods of treating anemia are provided, in which a human administered any of the foregoing antibodies or compositions and an erythropoiesis stimulator. Exemplary erythropoiesis stimulators include erythropoietin, erythropoietin variants and peptides or antibodies that bind and activate erythropoietin receptor. Other exemplary erythropoiesis stimulators include human erythropoietin of SEQ ID NO: 72 or darbepoetin alfa of SEQ ID NO: 73. Exemplary forms of anemia that may be treated according to such methods include anemia of inflammation, anemia of cancer, chemotherapy induced anemia, iron deficiency anemia, a disorder of iron homeostasis, ferroportin disease, or anemia resulting from kidney disease. Also provided are methods of treating a mammal with anemia that is hyporesponsive, or even resistant, to therapy with an erythropoiesis stimulator, comprising administering a therapeutically effective amount of an antibody that specifically binds human hepcidin. Any of the foregoing methods may also include administering iron to the subject.

The foregoing summary is not intended to define every aspect of the invention, and additional aspects are described in other sections, such as the Detailed Description. The entire document is intended to be related as a unified disclosure, and

it should be understood that all combinations of features described herein may be contemplated, even if the combination of features are not found together in the same sentence, or paragraph, or section of this document.

In addition to the foregoing, the invention can include, as an additional aspect, all embodiments of the invention narrower in scope in any way than the variations defined by specific paragraphs herein. For example, certain aspects of the invention that are described as a genus, and it should be understood that every member of a genus is, individually, an aspect of the invention. Also, aspects described as a genus or selecting a member of a genus, should be understood to embrace combinations of two or more members of the genus.

It should be understood that while various embodiments in the specification are presented using "comprising" language, under various circumstances, a related embodiment may also be described using "consisting of" or "consisting essentially of" language. It is to be noted that the term "a" or "an", refers to one or more, for example, "an immunoglobulin molecule," is understood to represent one or more immunoglobulin molecules. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

It should also be understood that when describing a range of values, the characteristic being described could be an individual value found within the range. For example, "a pH from about pH 4 to about pH 6," could be, but is not limited to, pH 4, 4.2, 4.6, 5.1 5.5 etc. and any value in between such values. Additionally, "a pH from about pH 4 to about pH 6," should not be construed to mean that the pH of a formulation in question varies 2 pH units in the range from pH 4 to pH 6 during storage, but rather a value may be picked in that range for the pH of the solution, and the pH remains buffered at about that pH. In some embodiments, when the term "about" is used, it means the recited number plus or minus 5%, 10%, 15% or more of that recited number. The actual variation intended is determinable from the context. Although the applicant(s) invented the full scope of the invention described herein, the applicants do not intend to claim subject matter described in the prior art work of others. Therefore, in the event that statutory prior art within the scope of a claim is brought to the attention of the applicants by a Patent Office or other entity or individual, the applicant(s) reserve the right to exercise amendment rights under applicable patent laws to redefine the subject matter of such a claim to specifically exclude such statutory prior art or obvious variations of statutory prior art from the scope of such a claim. Variations of the invention defined by such amended claims also are intended as aspects of the invention.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. **1**A-F show the off-rates for antibodies 1S1, 1S3, 2.7, 18B11, 23F11 and 26F11.

FIG. **2** shows murine anti-hepcidin antibody 2.7's functional ability to drive down intracellular iron concentrations in a beta-lactamase iron-response assay.

FIG. **3** shows the ability of human anti-hepcidin antibodies 18B11, 23F11 and 24E4 to drive down intracellular iron concentrations in a beta-lactamase iron-response assay

FIGS. **4**A-B demonstrate that an anti-hepcidin antibody neutralizes human hepcidin injected into mice.

FIGS. **5**A-E demonstrate that antibody neutralization of human hepcidin virally expressed mice restores normal early red cell characteristics.

FIGS. **6**A-B demonstrate that treatment with antibody 18B11 restored normal early red cell characteristics.

FIGS. **7**A-B demonstrate that treatment with antibody 18B11 leads to significant reduction in total hepcidin levels.

FIG. **8** shows a titration of adenovirus-associated virus (AAV)-mediated hepcidin expression and resulting serum iron concentrations.

FIG. **9** shows that viral overexpression of hepcidin causes hypo-responsiveness to erythropoietin.

FIGS. **10**A-E demonstrate that an anti-hepcidin antibody restores responsiveness to erythropoietin in mice virally overexpressing hepcidin.

FIGS. **11**A-C shows that neutralization of hepcidin by anti-hepcidin antibody treatment restores responsiveness to erythropoietin in human hepcidin knock-in mice with anemia of inflammation.

FIG. **12** demonstrates that hepcidin levels are elevated in anemia of cancer patients (AoC) and not in normal patients.

FIG. **13** demonstrates that hepcidin levels correlate with diagnosis of inflammatory anemia and not iron deficiency anemia.

FIG. **14**A shows a decision tree of iron indices and disease states for assessment of a patient, in the absence of hepcidin measurement.

FIG. **14**B shows a theoretical decision tree for assessment of a patient using measurement of hepcidin levels.

FIGS. **15**A-B show prohepcidin concentration measured by a sandwich immunoassay, demonstrating that prohepcidin is not detectable in serum.

FIG. **16** shows results of a Biacore experiment demonstrating that two monoclonal antibodies can bind to hepcidin at once.

FIG. **17** demonstrates that a sandwich ELISA can be constructed with monoclonal antibodies raised against mature hepcidin.

FIG. **18** shows the concentration of hepcidin present in buffer, rabbit serum and pooled human serum as determined by a competitive binding assay.

FIG. **19** shows the measurement of hepcidin in human sera.

FIG. **20** shows the concentration of hepcidin present in normal human sera using a competitive binding assay.

FIG. **21** shows the serum antibody concentration of antibodies 1S1 and 18B11 after administration of antibody-hepcidin complexes at various timepoints.

FIG. **22** shows the serum hepcidin concentration after administration of antibody-antigen complexes at various timepoints.

FIG. **23** shows the total urine hepcidin concentration mice pre-dosed with antibody 1S1 or 18B11 at various time points.

FIG. **24** shows the serum hepcidin concentration after administration of antibodies 18B11 and 1S1 at various timepoints.

FIG. **25** shows the serum hepcidin concentration in mice pre-dosed with antibody 1S1 and 18B11 at various timepoints.

FIG. **26** demonstrates that antibody 18B11 causes an accumulation of intracellular hepcidin.

DETAILED DESCRIPTION OF THE INVENTION

Described herein are antibodies that exhibit one or more properties that are associated with enhanced target antigen clearance from the circulation. Normally, antibodies are internalized into cells and then recycled back into circulation via a pathway involving the receptor FcRn (SEQ ID NO: 400). See, e.g., Prabhat et al., *Proc. Nat'l Acad. Sci.*, 104(14): 5889-5894 (2007). Antibodies (either alone or complexed with antigen) are internalized into the acidified endosomes of the cells. Some of these antibodies in the acidified endosomes

then bind to FcRn, which then recycles the antibodies and any associated antigen back out of the cell. Antibodies and/or antigen which did not bind to FcRn are transported to the lysosomes where they are degraded.

Antibodies are provided herein that exhibit differential pH binding to an antigen at a pH below about 7.4, as well as improved methods of treatment using such antibodies. For example, in some embodiments, such antibodies bind to antigen with at least about 50-fold to 1000-fold or more reduced binding affinity at a pH of about 5.5 or about 6 compared to a pH of about 7.4 (as measured by a 50-fold to 1000-fold or higher relative K_D at pH of about 5.5 or about 6 compared to at a pH of about 7.4). In some embodiments, the antibodies exhibit rapid off-rate for antigen of about 6×10^{-2} s^{-1} or higher, or about 1×10^{-1} s^{-1} or higher. Such antibodies are expected to bind antigen in circulation but tend to release the antigen in acidified endosomes at a pH of about 5.5 or about 6. The greater release of antigen in acidified lysosomes is associated with greater degradation of the target antigen and enhanced clearance of antigen. Another property may be greater recycling of free antibodies (unbound to antigen) into circulation to bind to additional antigen. In contrast, antibodies that do not release their antigen are more frequently recycled into circulation as an antibody-antigen complex, resulting in the inability of the antibody to bind to and ultimately clear additional antigen from circulation.

Also provided are antibodies that produce increased, e.g., at least 1.5-fold or 2-fold, intracellular accumulation of target antigen and/or enhanced clearance of antigen from circulation and/or reduced accumulation of circulating antigen, as well as improved methods of treatment using such antibodies. Other properties of such antibodies may include prevention of build-up of antibody-antigen complexes in circulation, making more recycled free antibody available to bind antigen than conventional antibodies, better potency, and reduced dose and/or frequency of administration to achieve therapeutic effectiveness.

Target antigens can include soluble antigens that have a relatively high level of production and/or a short half-life in circulation of about 24 hours or less, or about 18, 12, 8, 4, 3, 2, or 1 hour or less, or about 45, 30, or 15 minutes or less. Antibodies will generally bind to the target antigen with a K_D in the range of 1×10^{-6}M or less, or ranging down to 10^{-16} M or lower, (e.g., about 10^{-6}, about 10^{-7}, about 10^{-8}, about 10^{-9}, about 10^{-10}, about 10^{-11}, about 10^{-12}, about 10^{-13}, about 10^{-14}, about 10^{-15}, about 10^{-16} or less), where lower K_D indicates better affinity.

Also provided are methods of screening for antibodies with desired properties comprising identifying an antibody that exhibits differential pH binding to an antigen at a pH below about 7.4, and optionally demonstrating that the antibody exhibits enhanced target antigen clearance relative to an antibody of similar or better binding affinity that does not exhibit differential pH binding, and/or optionally demonstrating that the antibody exhibits increased intracellular accumulation of target antigen and/or reduced accumulation of circulating antigen relative to an antibody of similar or better binding affinity that does not exhibit differential pH binding.

In another aspect, methods of treatment are provided that involve administering therapeutically effective amounts of antibodies with the above-described properties, optionally also involving detecting circulating blood level of a target antigen before or concurrent with said administration, and detecting circulating blood level of said target antigen after said administration, e.g. about 24 hours, 2 days, 3, 4, 5, 6, 7 days, or 2 weeks after said administration.

Hepcidin is a good target antigen for antibodies that exhibit the properties described herein. Hepcidin has a relatively short half-life (Rivera et al., *Blood,* 106:2196-2199, 2005). The human hepcidin gene encodes an 84 residue pre-propeptide (SEQ ID NO: 8). The corresponding cDNA and genomic sequences are set forth in SEQ ID NOs: 7 and 100, respectively. The 24-residue N-terminal signal peptide (residues 1-24 of SEQ ID NO: 8) is first cleaved to produce prohepcidin, which is then further processed by cleavage of the prodomain (residues 25-59 of SEQ ID NO: 8) to produce the 25-residue mature hepcidin (residues 60-84 of SEQ ID NO: 8, set forth in SEQ ID NO: 9). In addition to the primary 25 amino acid form, further N-terminally truncated forms that are 20 or 22 amino acids in length can be identified in urine (20 amino acids, SEQ ID NO: 96; and 22 amino acids, SEQ ID NO: 98). Mature human hepcidin contains eight cysteine residues, which are referred to herein sequentially as C1 through C8 (numbered from the N-terminus to the C-terminus).

In some embodiments, the antibodies described herein bind to mature, correctly folded, bioactive human hepcidin in which disulfide bonds are formed between C1-C8, C2-C4, C3-C6 and C5-C7, with the desired affinity. In some embodiments, the antibodies inhibit the iron-regulating activity of hepcidin. In some embodiments, the monoclonal antibody decreases intracellular iron concentration and/or increases circulating iron concentration at an EC_{50} of about 10^{-8} M or less, or about 20 nM or less. In some embodiments, the antibody exhibits the property in mammals of increasing red blood cell count (number) or hemoglobin or hematocrit levels, and/or normalizing reticulocyte count, reticulocyte mean cell volume and/or reticulocyte hemoglobin content, increases circulating iron level or Tsat in a mouse overexpressing human hepcidin for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 days or longer after a single dose of the antibody.

Anti-Hepcidin Antibodies and Specific Binding Agents

The term "antibody" is used in the broadest sense and includes fully assembled antibodies, monoclonal antibodies, polyclonal antibodies, multispecific antibodies (including bispecific antibodies), antibody fragments that can bind an antigen (including, Fab', $F'(ab)_2$, Fv, single chain antibodies, diabodies), and recombinant peptides comprising the foregoing as long as they exhibit the desired biological activity. Multimers or aggregates of intact molecules and/or fragments, including chemically derivatized antibodies, are contemplated. Antibodies of any isotype class or subclass, including IgG, IgM, IgD, IgA, and IgE, IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2, or any allotype, are contemplated. Different isotypes have different effector functions; for example, IgG1 and IgG3 isotypes have antibody-dependent cellular cytotoxicity (ADCC) activity.

In some embodiments, the antibodies described herein exhibit differential pH binding to an antigen. The term "differential pH binding" as used herein refers to an antibody that binds to its antigen with high affinity (lower K_D) at a pH of about 7.4 but binds to the antigen with a lower affinity (higher K_D) at a lower pH. An antibody that exhibits a K_D that is at least 50, at least 60, at least 70, at least 80, at least 90, at least 100, at least 150, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, at least 1000-fold or more higher for its antigen at a pH more acidic than a pH of about 7.4 (e.g., a pH of about 7.0, about 6.5, about 6.0, about 5.5, about 5.0 or about 4.5) is specifically contemplated.

The term "binding affinity" or "affinity" as used herein refers to the equilibrium dissociation constant (K_D) associ-

ated with each antigen-antibody interaction. In some embodiments, the antibodies described herein exhibit desirable properties such as binding affinity as measured by K_D for hepcidin in the range of 1×10^{-6} M or less, or ranging down to 10^{-16} M or lower, (e.g., about 10^{-6}, 10^{-7},10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13}, 10^{-14}, 10^{-15}, 10^{-16} M or less) at about pH 7.4, where lower K_D indicates better affinity. Optionally the antibody further exhibits a K_D for hepcidin at least 50-1000 fold higher (less binding affinity) at about pH 5.5 or about pH 6 compared to at a pH of about 7.4. The equilibrium dissociation constant can be determined in solution equilibrium assay using BIAcore and/or KinExA, such as described in Examples 3 and 4.

The binding affinity is directly related to the ratio of the kinetic off-rate (generally reported in units of inverse time, e.g. seconds^{-1}) divided by the kinetic on-rate (generally reported in units of concentration per unit time, e.g. M/s). Off-rate analysis can estimate the interaction that occurs in vivo, since a slow off-rate would predict a greater degree of interaction over long period of time. In some embodiments, the antibodies described herein exhibit an off-rate of about $6\times10^{-2}s^{-1}$ or higher, or about 1×10^{-1} s^{-1} or higher (faster off-rate) at about pH 5.5 or about pH 6. Optionally, the antibody also exhibits an off rate of $1\times10^{-3}s^{-1}$ or less (slower off-rate) at about pH 7.4. In other embodiments, the antibodies described herein exhibit an off-rate (measured in s^{-1}) that is at least about 10-fold, 20, 30, 40, 50, 60, 70, 80, 90 or 100-fold higher at about pH 5.5 or about pH 6 compared to the off-rate at about pH 7.4.

In other embodiments, the antibodies described herein exhibit specificity for or specifically bind to human hepcidin. As used herein, an antibody is "specific for" or "specifically binds" human hepcidin when it has a significantly higher binding affinity for, and consequently is capable of distinguishing, human hepcidin compared to other unrelated proteins in different families. In some embodiments, such antibodies may also cross-react with hepcidin of other species, such as murine, rat, or primate hepcidin; while in other embodiments, the antibodies bind only to human or primate hepcidin and not significantly to rodent hepcidin. In some embodiments, antibodies bind to human and cynomologous monkey hepcidin but not significantly to rodent hepcidin. In some embodiments, antibodies specific for hepcidin cross-react with other proteins in the same family, while in other embodiments, the antibodies distinguish hepcidin from other related family members, including defensins or mouse hepc2.

In some embodiments, the antibodies exhibit "enhanced target antigen clearance", meaning they produce a faster or greater reduction in circulating blood levels of total target antigen. For example, enhanced antigen clearance compared to an antibody that does not exhibit differential pH binding can be measured by comparing blood levels of target antigen at a certain time point, e.g. about 12, 24, 36, 48, or 72 hours after administration of antibody. Enhanced antigen clearance will result in greater reduction in blood level at the same time point. Alternatively, for example, enhanced antigen clearance can be measured by comparing the time period required to reduce target antigen to, e.g., 25%, 50%, 75% or 90% of its blood level prior to administration of antibody. Enhanced antigen clearance will result in a shorter time period to achieve such reduction. As yet another alternative, enhanced antigen clearance is indicated by greater internalization of target antigens into cells expressing FcRn, as measured by intracellular accumulation of target antigen.

In yet other embodiments, the monoclonal antibodies inhibit (or neutralize) hepcidin iron-regulating activity, in vitro and or in vivo. Such hepcidin-neutralizing antibodies are therapeutically useful for hepcidin-related disorders or disorders of iron homeostasis. Hepcidin neutralizing activity can be measured through a number of markers, for example, ferritin/iron levels, red blood cell count, red blood cell characteristics (hemoglobin content and/or cell volume), early red blood cell characteristics (reticulocyte numbers, hemoglobin content or cell volume) (Clinical Hematology, third edition, Lippincott, Williams and Wilkins; editor Mary L. Turgeon, 1999) ferroportin internalization, or iron transport. In one embodiment, the monoclonal antibody decreases intracellular iron concentration at an EC_{50} of about 10^{-8} M or less and/or increases circulating iron concentration.

In some embodiments, a monoclonal antibody as described herein antagonizes the effect of human hepcidin or inhibits hepcidin iron-regulating activity. In some embodiments, a monoclonal antibody as described herein exerts an effect at an EC_{50} of about 1×10^{-8} M or less, or about 1×10^{-7} M or less. For example, an antibody may decrease the intracellular iron level in a cell at an EC_{50} of about 1×10^{-8} M or less, or may reduce ferritin expression at an EC_{50} of about 1×10^{-8} M or less, as determined by a ferritin assay. In other embodiments, a monoclonal antibody as described herein may reduce free serum hepcidin levels by at least about 20%, by at least about 30%, by at least about 40%, by at least about 50%, by at least about 60%, by at least about 70%, by at least about 80%, or by at least about 90%. In other embodiments, a monoclonal antibody as described herein may increase red blood cell count (number), red blood cell mean cell volume or red blood cell hemoglobin content, increase hemoglobin, increase hematocrit, increase Tsat, increase circulating (or serum) iron levels, and/or increase or normalize reticulocyte count, reticulocyte mean cell volume, reticulocyte hemoglobin content or reticulocyte numbers.

In some embodiments, the invention contemplates: 1) a monoclonal antibody that retains any one, two, three, four, five, or six of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 or CDRL3 of any of antibody Ab43, 2.7, 2.41, R9, 1C9, 1S1, 1S2, 1S3, 1S4, 1S5, 3B3; 4E1, 7A3, 9D12, 12B9, 15E1, 18B11, 18D8, 19B8, 19C1, 19D12, 19H6, 20E12, 22F12, 22H10, 23A11, 23F11, 24E4 and 26F11, optionally including one or two mutations in such CDR(s), wherein the antibody exhibits differential pH binding, and/or rapid off rate (e.g., 6×10^{-2} s^{-1} or higher) at a pH of about 5.5 or about 6, and/or enhanced hepcidin clearance; 2) a monoclonal antibody that retains all of CDRH1, CDRH2, CDRH3, or the heavy chain variable region of any of antibody Ab43, 2.7, 2.41, R9, 1C9, 1S1, 1S2, 1S3, 1S4, 1S5, 3B3; 4E1, 7A3, 9D12, 12B9, 15E1, 18B11, 18D8, 19B8, 19C1, 19D12, 19H6, 20E12, 22F12, 22H10, 23A11, 23F11, 24E4 and 26F11, optionally including one or two mutations in such CDR(s), wherein the antibody exhibits differential pH binding, and/or rapid off rate (e.g., 6×10^{-2} s^{-1} or higher) at a pH of about 5.5 or about 6, and/or enhanced hepcidin clearance; 3) a monoclonal antibody that retains all of CDRL1, CDRL2, CDRL3, or the light chain variable region of any of antibody Ab43, 2.7, 2.41, R9, 1C9, 1S1, 1S2, 1S3, 1S4, 1S5, 3B3; 4E1, 7A3, 9D12, 12B9, 15E1, 18B11, 18D8, 19B8, 19C1, 19D12, 19H6, 20E12, 22F12, 22H10, 23A11, 23F11, 24E4 and 26F11, optionally including one or two mutations in such CDR(s), wherein the antibody exhibits differential pH binding, and/or rapid off rate (e.g., 6×10^{-2} s^{-1} or higher) at a pH of about 5.5 or about 6, and/or enhanced hepcidin clearance; 4) a monoclonal antibody that binds to the same epitope of mature human hepcidin as antibody Ab43, 2.7, 2.41, R9, 1C9, 1S1, 1S2, 1S3, 1S4, 1S5, 3B3; 4E1, 7A3, 9D12, 12B9, 15E1, 18B11, 18D8, 19B8, 19C1, 19D12, 19H6, 20E12, 22F12, 22H10, 23A11, 23F11, 24E4 and 26F11, e.g. as determined through X-ray crystallography,

or a conformational epitope comprising an amino acid within amino acids 1-5 of SEQ ID NO: 9 and/or an amino acid within a loop formed by amino acids 10-13 of SEQ ID NO: 9 and/or an amino acid within a loop formed by amino acids 14-22 of SEQ ID NO: 9, wherein the antibody exhibits differential pH binding, and/or rapid off rate (e.g., 6×10^{-2} s^{-1} or higher) at a pH of about 5.5 or about 6, and/or enhanced hepcidin clearance; 5) a monoclonal antibody that competes with antibody Ab43, 2.7, 2.41, R9, 1C9, 1S1, 1S2, 1S3, 1S4, 1S5, 3B3; 4E1, 7A3, 9D12, 12B9, 15E1, 18B11, 18D8, 19B8, 19C1, 19D12, 19H6, 20E12, 22F12, 22H10, 23A11, 23F11, 24E4 and 26F11 for binding to mature human hepcidin by more than about 75%, more than about 80%, or more than about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94% or 95% (e.g., assessed by competitive ELISA or Biacore or by other methods known in the art), wherein the antibody exhibits differential pH binding, and/or rapid off rate (e.g., 6×10^{-2} s^{-1} or higher) at a pH of about 5.5 or about 6, and/or enhanced hepcidin clearance; 6) a monoclonal antibody that specifically binds to human hepcidin of SEQ ID NO: 9 with an affinity K_D (equilibrium dissociation constant) for hepcidin in the range of 1×10^{-8} M or less, or ranging down to 10^{-16} M or lower, (e.g., about 10^{-8}, 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13}, 10^{-14}, 10^{-15}, 10^{-16} M or less) as measured by BIAcore or KinExA and that exhibits at least one, two, three or more of the properties selected from the group consisting of: i) differential pH binding as shown by at least about 50-1000 fold lower affinity (or higher K_D) at a pH of about 5.5 or about 6 compared to at about pH 7.4; ii) at least about 5, 6, 7, 8, 9, or 10-fold faster clearance of said hepcidin compared to antibody 1S1; iii) a rapid off rate as measured by, e.g., an off-rate of about 6×10^{-2} s^{-1} or higher at about pH 5.5 or about pH 6, or an off-rate of about 1×10^{-1} s^{-1} or higher at about pH 5.5 or about pH 6, or an off rate of at least about 10-fold, 20, 30, 40, 50, 60, 70, 80, 90 or 100-fold higher at about pH 5.5 or about 6 compared to the off-rate at about pH 7.4; iv) reduces the level of total human hepcidin in serum by at least about 90% in a C57BL/6 mouse about 24 hours after the administration to said mouse of (i) a 1 mg dose of said antibody and (ii) a pre-complexed single dose of 3.7 μg of human hepcidin with a 1 mg dose of said antibody; v) reduces the level of total human hepcidin in serum in a mouse by at least about 90% about 24 hours after said mouse is administered a single dose of 3.7 μg of human hepcidin, wherein said hepcidin is administered three days after said mouse is pre-dosed with said antibody; vi) produces at least about 1.5-fold or 2-fold higher intracellular accumulation of human hepcidin in FcRn-transfected HEK293 cells compared to antibody 1S1; vii) results in a greater than about 50% reduction in overall accumulation of total serum hepcidin in mice treated with said antibody compared to antibody 1S1, e.g., at about 24 hours; and/or viii) increases circulating iron level or Tsat in a mouse expressing hepcidin for at least about 1 day, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11 days or more after a single dose of the antibody.

In some embodiments, an antibody described herein exhibits differential pH binding as shown by at least about 50-1000 fold lower affinity (higher K_D) at a pH of about 5.5 or about 6 compared to at about pH 7.4 and also exhibits (1) at least about 5, 6, 7, 8, 9, or 10-fold faster clearance of said hepcidin compared to antibody 1S1; and/or (2) a rapid off rate of, e.g., about 6×10^{-2} s^{-1} or higher at about pH 5.5 or about pH 6; and/or (3) reduces the level of total human hepcidin in serum by at least about 90% in a C57BL/6 mouse about 24 hours after the administration to said mouse of (i) a 1 mg dose of said antibody and (ii) a pre-complexed single dose of 3.7 μg of human hepcidin with a 1 mg dose of said antibody; and/or (4) reduces the level of total human hepcidin in serum in a mouse by at least about 90% about 24 hours after said mouse is administered a single dose of 3.7 μg of human hepcidin, wherein said hepcidin is administered three days after said mouse is pre-dosed with said antibody; and/or (5) further produces at least about 1.5-fold or 2-fold higher intracellular accumulation of human hepcidin in FcRn-transfected HEK293 cells compared to antibody 1S1; and/or (6) results in a greater than about 50% reduction in overall accumulation of total serum hepcidin in mice treated with said antibody compared to antibody 1S1; and/or (7) increases circulating iron level or Tsat in a mouse expressing hepcidin for at least about 1 day, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11 days or more after a single dose of the antibody.

In some embodiments, an antibody described herein exhibits at least about 5, 6, 7, 8, 9, or 10-fold faster clearance of said hepcidin compared to antibody 1S1 and also (1) reduces the level of total human hepcidin in serum by at least about 90% in a C57BL/6 mouse about 24 hours after the administration to said mouse of (i) a 1 mg dose of said antibody and (ii) a pre-complexed single dose of 3.7 μg of human hepcidin with a 1 mg dose of said antibody; and/or (2) reduces the level of total human hepcidin in serum in a mouse by at least about 90% about 24 hours after said mouse is administered a single dose of 3.7 μg of human hepcidin, wherein said hepcidin is administered three days after said mouse is pre-dosed with said antibody; and/or (3) produces at least about 1.5-fold or 2-fold higher intracellular accumulation of human hepcidin in FcRn-transfected HEK293 cells compared to antibody 1S1; and/or (4) results in a greater than about 50% reduction in overall accumulation of total serum hepcidin in mice treated with said antibody compared to antibody 1S1 and/or (5) increases circulating iron level or Tsat in a mouse expressing hepcidin for at least about 1 day, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11 days or more after a single dose of the antibody.

In some embodiments, the antibody exhibits a rapid off-rate, e.g., about 6×10^{-2} s^{-1} or higher at about pH 5.5 or about pH 6 and also (1) reduces the level of total human hepcidin in serum by at least about 90% in a C57BL/6 mouse about 24 hours after the administration to said mouse of (i) a 1 mg dose of said antibody and (ii) a pre-complexed single dose of 3.7 μg of human hepcidin with a 1 mg dose of said antibody; and/or (2) reduces the level of total human hepcidin in serum in a mouse by at least about 90% about 24 hours after said mouse is administered a single dose of 3.7 μg of human hepcidin, wherein said hepcidin is administered three days after said mouse is pre-dosed with said antibody; and/or (3) produces at least about 1.5-fold or 2-fold higher intracellular accumulation of human hepcidin in FcRn-transfected HEK293 cells compared to antibody 1S1; and/or (4) results in a greater than about 50% reduction in overall accumulation of total serum hepcidin in mice treated with said antibody compared to antibody 1S1; and/or (5) increases circulating iron level or Tsat in a mouse expressing hepcidin for at least about 1 day, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11 days or more after a single dose of the antibody.

In some embodiments, an antibody described herein reduces the level of total human hepcidin in serum in a mouse by at least about 90% about 24 hours after said mouse is administered a single dose of 3.7 μg of human hepcidin, wherein said hepcidin is administered three days after said mouse is pre-dosed with said antibody, and also (1) produces at least about 1.5-fold or 2-fold higher intracellular accumu-

lation of human hepcidin in FcRn-transfected HEK293 cells compared to antibody 1S1; and/or (2) results in a greater than about 50% reduction in overall accumulation of total serum hepcidin in mice treated with said antibody compared to antibody 1S1; and/or (3) increases circulating iron level or Tsat in a mouse expressing hepcidin for at least about 1 day, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11 days or more after a single dose of the antibody.

In some embodiments, an antibody described herein produces at least about 1.5-fold or 2-fold higher intracellular accumulation of human hepcidin in FcRn-transfected HEK293 cells compared to antibody 1S1 and also results in a greater than about 50% reduction in overall accumulation of total serum hepcidin in mice treated with said antibody compared to antibody 1S1; and/or increases circulating iron level or Tsat in a mouse expressing hepcidin for at least about 1 day, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11 days or more after a single dose of the antibody.

In another aspect, methods are provided for modifying antibodies that lack properties such as differential pH binding and/or enhanced target antigen clearance) to produce antibodies that exhibit such properties. The antibody can be an anti-hepcidin antibody produced by such methods. In some embodiments, residues in the CDRs and/or residues that according to three-dimensional modeling are predicted to be most affected by introduction of an amino acid with a pKa in the range of pH of about 5.5 to about 7.4 are mutated by the introduction of such an amino acid, e.g. histidine. Histidine is an amino acid that is sensitive to pH shifts from 7.4 to 6.0, as the imidazole side chain of histidine has a pKa just over 6, which may vary slightly higher or lower depending on the environment of the amino acid. Upon a change in pH from about 7.4 to a lower pH of about 6.0 or 5.5, for example, the mutated antibody may undergo an allosteric conformational change that would disrupt antigen-antibody interaction.

Candidate residues for mutation include residues that are directed contact sites with antigen or sites that contribute to the formation of charge-charge interactions along the antibody-antigen binding interface. Other candidate residues include residues within conserved regions of the antibody. Yet other candidate residues include framework residues that are at least 10% surface exposed and within 4.5 Å of a CDR residue. Additional candidate residues include those selected by visual inspection of a 3-dimensional structural model for amino acids in proximity to the CDRs or selected framework residues. Histidine or other desired amino acids can be mutated at single or multiple positions within the amino acid sequence. For example, mutations which produce some differential pH binding effect as single mutations can be combined as double, triple or more multiple mutations. Antibodies that have been mutated in such a manner are then screened for differential pH binding and then can be further screened for other properties.

In one aspect, at least one, two, three, four, five, six or more residues in the heavy chain variable region of said antibody are deleted and replaced with a histidine residue. In another aspect, at least one, two, three, four, five, six or more residues in the light chain variable region of said antibody are deleted and replaced with a histidine residue. In some aspects, at least one residue from the light chain variable region of said antibody and at least one residue from the heavy chain variable region of said antibody is replaced with a histidine residue. In one embodiment, at least one residue in the heavy chain variable region at a position selected from the group consisting of 52, 57, 99 and 107 of SEQ ID NO: 170 is replaced with a histidine residue. In another embodiment, at least one residue in the light chain variable region at a position selected from the group consisting of 27 and 89 of SEQ ID NO: 168 is replaced with a histidine residue. In another embodiment, the amino acids at positions 57 and 107 of the heavy chain variable region of SEQ ID NO: 170 are replaced with a histidine residue. In another embodiment, the amino acids at position 107 of the heavy chain variable region of SEQ ID NO: 170 and position 27 of the light chain variable region of SEQ ID NO: 168 are replaced with a histidine. In another embodiment, the amino acid at position 107 of the heavy chain variable region of SEQ ID NO: 170 and the amino acid at position 89 of the light chain variable region of SEQ ID NO: 168 is replaced with a histidine. In another embodiment, the amino acid at positions 99 and 107 of the heavy chain variable region of SEQ ID NO: 170 are replaced with a histidine.

In one embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 16-21 (Ab 43). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 28-33 (2.7 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 40-45 (2.41 CDRs). In yet another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 52-57 (R9 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 111-116 (1C9 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 121-126 (3B3 CDRs). In yet another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 131-136 (4E1 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 141-146 (7A3 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 151-156 (9D12 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 161-166 (12B9 CDRs). In yet another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 171-176 (15E1 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 334-339 (18B11 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 314-319 (18D8 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 344-349 (19B8 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 324-329 (19C1 CDRs). In yet another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 294-299

(19D12 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 304-309 (19H6 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 354-359 (20E12 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 364-369 (22F12 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 374-379 (22H10 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 384-389 (23A11 CDRs). In yet another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 181-186 (23F11 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 394-399 (24E4 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 191-196 (26F11 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 203-205 and 131-133 (1S1 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 214-216 and 144-146 (1S2 CDRs). In yet another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 225-227 and 164-166 (1S3 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 236-238 and 174-176 (1S4 CDRs). In another embodiment, the antibody comprises at least one, two, three, four, five or all of the amino acid sequences selected from the group consisting of SEQ ID NOs: 247-249 and 184-186 (1S5 CDRs).

In some embodiments, the antibody comprises all three light chain CDRs, all three heavy chain CDRs, or all six CDRs. In some embodiments, two light chain CDRs from an antibody may be combined with a third light chain CDR from a different antibody. Alternatively, a CDRL1 from one antibody can be combined with a CDRL2 from a different antibody and a CDRL3 from yet another antibody, particularly where the CDRs are highly homologous. Similarly, two heavy chain CDRs from an antibody may be combined with a third heavy chain CDR from a different antibody; or a CDRH1 from one antibody can be combined with a CDRH2 from a different antibody and a CDRH3 from yet another antibody, particularly where the CDRs are highly homologous.

Consensus CDRs may also be used. In one embodiment, the antibody comprises one or more of the amino acid sequences set forth in SEQ ID NO: 74 (XASNLES), SEQ ID NO: 75 (XQSNEE) and SEQ ID NO: 76 (QQXNEX), SEQ ID NO: 28 (RASESVDSYGNSFMH), SEQ ID NO: 77 (WINTXSGVPTYADDFXG), SEQ ID NO: 78 (XXYYGX*A*Y), SEQ ID NO: 19 (TYGMS), SEQ ID NO: 284 (VIXYXXSNKYYADSVKG), SEQ ID NO: 285 (WIXAXNGXXXXAXXXQX), SEQ ID NO: 286 (AQEGXAPDAFDI), SEQ ID NO: 287 (QAWYSSTNVX), SEQ ID NO: 288 (QAWDSSTAXX), SEQ ID NO: 289 (QSDYSSXXX**), wherein X is any amino acid and * can be absent or any amino acid.

In yet another embodiment, the antibody comprises the light and/or heavy chain variable region of an antibody, e.g., SEQ ID NO: 15 (Ab43 heavy chain variable region), and/or SEQ ID NO: 13 (Ab43 light chain variable region); SEQ ID NO: 27 (2.7 heavy chain variable region), and/or SEQ ID NO: 25 (2.7 light chain variable region); SEQ ID NO: 39 (2.41 heavy chain variable region), and/or SEQ ID NO: 37 (2.41 light chain variable region); or SEQ ID NO: 51 (R9 heavy chain variable region), and/or SEQ ID NO: 49 (R9 light chain variable region), SEQ ID NO: 110 (1C9 heavy chain variable region) and/or SEQ ID NO: 108 (1C9 light chain variable region); or SEQ ID NO: 120 (3B3 heavy chain variable region) and/or SEQ ID NO: 118 (3B3 light chain variable region); SEQ ID NO: 130 (4E1 heavy chain variable region) and/or SEQ ID NO: 128 (4E1 light chain variable region); or SEQ ID NO: 140 (7A3 heavy chain variable region) and/or SEQ ID NO:138 (7A3 light chain variable region); or SEQ ID NO: 150 (9D12 heavy chain variable region) and/or SEQ ID NO: 148 (9D12 light chain variable region); SEQ ID NO: 160 (12B9 heavy chain variable region), and/or SEQ ID NO: 158 (12B9 light chain variable region); SEQ ID NO: 170 (15E1 heavy chain variable region) and/or SEQ ID NO: 168 (15E1 light chain variable region); SEQ ID NO: 333 (18B11 heavy chain variable region) and/or SEQ ID NO: 331 (18B11 light chain variable region); SEQ ID NO: 313 (18D8 heavy chain variable region) and/or SEQ ID NO: 311 (18D8 light chain variable region); SEQ ID NO: 343 (19B8 heavy chain variable region) and/or SEQ ID NO: 341 (19B8 light chain variable region); SEQ ID NO: 323 (19C1 heavy chain variable region) and/or SEQ ID NO: 321 (19C1 light chain variable region); SEQ ID NO: 293 (19D12 heavy chain variable region) and/or SEQ ID NO: 291 (19D12 light chain variable region); SEQ ID NO: 303 (19H6 heavy chain variable region) and/or SEQ ID NO: 301 (191-16 light chain variable region); SEQ ID NO: 353 (20E12 heavy chain variable region) and/or SEQ ID NO: 351 (20E12 light chain variable region); SEQ ID NO: 363 (22F12 heavy chain variable region) and/or SEQ ID NO: 361 (22F12 light chain variable region); SEQ ID NO: 373 (22H10 heavy chain variable region) and/or SEQ ID NO: 371 (22H10 light chain variable region); SEQ ID NO: 383 (23A11 heavy chain variable region) and/or SEQ ID NO: 381 (23A11 light chain variable region); SEQ ID NO: 180 (23F11 heavy chain variable region) and/or SEQ ID NO: 178 (23F11 light chain variable region); 393 (24E4 heavy chain variable region) and/or SEQ ID NO: 391 (24E4 light chain variable region); SEQ ID NO: 190 (26F11 heavy chain variable region) and/or SEQ ID NO: 188 (26F11 light chain variable region); or SEQ ID NO: 202 (1S1 heavy chain variable region) and/or SEQ ID NO: 128 (1S1 light chain variable region); SEQ ID NO: 213 (1S2 light chain variable region) and/or SEQ ID NO: 140 (1S2 heavy chain variable region); SEQ ID NO: 224 (1S3 light chain variable region) and/or SEQ ID NO: 160 (1S3 heavy chain variable region); SEQ ID NO: 235 (1S4 light chain variable region) and/or SEQ ID NO: 170 (1S4 heavy chain variable region; or SEQ ID NO: 246 (1S5 light chain variable region) and/or SEQ ID NO: 190 (1S5 heavy chain variable region).

In some embodiments, an antibody is provided that comprises a polypeptide having an amino acid sequence at least about 65%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from the group consisting of SEQ ID NOs:

(Ab43 heavy chain variable region), 27 (2.7 heavy chain variable region), 39 (2.41 heavy chain variable region), 51 (R9 heavy chain variable region), 110 (1C9 heavy chain variable region), 120 (3B3 heavy chain variable region), 130 (4E1 heavy chain variable region), 140 (7A3 heavy chain variable region), 150 (9D12 heavy chain variable region), 160 (12B9 heavy chain variable region), 170 (15E1 heavy chain variable region), 333 (18B11 heavy chain variable region), 313 (18D8 heavy chain variable region), 343 (19B8 heavy chain variable region), 323 (19C1 heavy chain variable region), 293 (19D12 heavy chain variable region), 303 (19H6 heavy chain variable region), 353 (20E12 heavy chain variable region), 363 (22F12 heavy chain variable region), 373 (22H10 heavy chain variable region), 383 (23A11 heavy chain variable region), 180 (23F11 heavy chain variable region), 393 (24E4 heavy chain variable region), 190 (26F11 heavy chain variable region), 202 (1S1 heavy chain variable region), 13 (Ab43 light chain variable region), 25 (2.7 light chain variable region), 37 (2.41 light chain variable region), 49 (R9 light chain variable region), 108 (1C9 light chain variable region), 118 (3B3 light chain variable region), 128 (4E1 light chain variable region), 138 (7A3 light chain variable region), 148 (9D12 light chain variable region), 158 (12B9 light chain variable region), 168 (15E1 light chain variable region), 331 (18B11 light chain variable region), 311 (18D8 light chain variable region), 341 (19B8 light chain variable region), 321 (19C1 light chain variable region), 291 (19D12 light chain variable region), 301 (19H6 light chain variable region), 351 (20E12 light chain variable region), 361 (22F12 light chain variable region), 371 (22H10 light chain variable region), 381 (23A11 light chain variable region), 178 (23F11 light chain variable region), 391 (24E4 light chain variable region), 188 (26F11 light chain variable region), 213 (1S2 light chain variable region), 224 (1S3 light chain variable region), 235 (1S4 light chain variable region), 246 (1S5 light chain variable region), the polypeptide further comprising at least one or more of the amino acid sequences set forth in SEQ ID NOs: 16-21 (Ab43 CDRs), 28-33 (2.7CDRs), 40-45 (2.41 CDRs), 52-57 (R9 CDRs), 111-116 (1C9 CDRs), 121-126 (3B3 CDRs), 131-136 (4E1 CDRs), 141-146 (7A3 CDRs), 151-156 (9D12 CDRs), 161-166 (12B9 CDRs), 171-176 (15E1 CDRs), 334-339 (18B11 CDRs), 314-319 (18D8 CDRs), 344-349 (19B8 CDRs), 324-329 (19C1 CDRs), 294-299 (19D12 CDRs), 304-309 (19H6 CDRs), 354-359 (20E12 CDRs), 364-369 (22F12 CDRs), 374-379 (22H10 CDRs), 384-389 (23A11 CDRs), 181-186 (23F11 CDRs), 394-399 (24E4 CDRs), 191-196 (26F11 CDRs), 203-205 (1S1 light chain CDRs) and 131-133 (1S1 heavy chain CDRs), 214-216 (1S2 heavy chain CDRs) and 144-146 (1S2 light chain CDRs), 225-227 (1S3 heavy chain CDRs) and 164-166 (1S3 light chain CDRs), 236-238 (1S4 heavy chain CDRs) and 174-176 (1S4 light chain CDRs), 247-249 (1S5 heavy chain CDRs) and 184-186 (1S5 light chain CDRs). In any of the foregoing embodiments, the polypeptide includes a sequence comprising one or two modifications to any of the amino acid sequences set forth in SEQ ID NOs: 16-21 (Ab43 CDRs), 28-33 (2.7CDRs), 40-45 (2.41 CDRs), 52-57 (R9CDRs), 111-116 (1C9 CDRs), 121-126 (3B3 CDRs), 131-136 (4E1 CDRs), 141-146 (7A3 CDRs), 151-156 (9D12 CDRs), 161-166 (12B9 CDRs), 171-176 (15E1 CDRs), 334-339 (18B11 CDRs), 314-319 (18D8 CDRs), 343-349 (1988 CDRs), 324-329 (19C1 CDRs), 294-299 (19D12 CDRs), 304-309 (19H6 CDRs), 354-359 (20E12 CDRs), 364-369 (22F12 CDRs), 374-379 (22H10 CDRs), 384-389 (23A11 CDRs), 181-186 (23F11 CDRs), 394-399 (24E4 CDRs), 191-196 (26F11 CDRs), 203-205 (1S1 light chain CDRs) and 131-133 (1S1 heavy chain CDRs), 214-216 (1S2 heavy chain CDRs) and 144-146 (1S2 light chain CDRs), 225-227 (1S3 heavy chain CDRs) and 164-166 (1S3 light chain CDRs), 236-238 (1S4 heavy chain CDRs) and 174-176 (1S4 light chain CDRs), 247-249 (1S5 heavy chain CDRs) and 184-186 (1S5 light chain CDRs).

In some embodiments, the antibody comprises the heavy chain variable region of any of antibodies Ab43, 2.7, 2.41, R9, 1C9, 1S1, 1S2, 1S3, 1S4, 1S5, 3B3; 4E1, 7A3, 9D12, 12B9, 15E1, 18B11, 18D8, 19B8, 19C1, 19D12, 19H6, 20E12, 22F12, 22H10, 23A11, 23F11, 24E4 and 26F11 and optionally comprises a constant region selected from the group consisting of a human IgG1 heavy chain constant region (SEQ ID NOs: 401-402) and a human IgG2 heavy chain constant region (SEQ ID NOs: 403-404). In some embodiments, the antibody comprises the light chain variable region of any of antibodies Ab43, 2.7, 2.41, R9, 1C9, 1S1, 1S2, 1S3, 1S4, 1S5, 3B3; 4E1, 7A3, 9D12, 12B9, 15E1, 18B11, 18D8, 19B8, 19C1, 19D12, 19H6, 20E12, 22F12, 22H10, 23A11, 23F11, 24E4, and 26F11 and optionally comprises a human kappa light chain constant region (SEQ ID NOs: 405-406). In another embodiment, the antibody comprises the light chain variable region of any of antibodies Ab43, 2.7, 2.41, R9, 1C9, 1S1, 1S2, 1S3, 1S4, 1S5, 3B3; 4E1, 7A3, 9D12, 12B9, 15E1, 18B11, 18D8, 19B8, 19C1, 19D12, 19H6, 20E12, 22F12, 22H10, 23A11, 23F11, 24E4 and 26F11 and optionally comprises a constant region selected from the group consisting of a human lambda light chain constant region type C1 (SEQ ID NOs: 407-408), a human lambda light chain constant region type C2 (SEQ ID NOs: 409-410), a human lambda light chain constant region type C3 (SEQ ID NOs: 411-412), a human lambda light chain constant region type C6 (SEQ ID NOs: 413-414) and a human lambda light chain constant region type C7 (SEQ ID NO: 415-416).

The cDNA and amino acid sequences for the full length light and heavy chains of each of antibodies 1C9, 3B3, 4E1, 7A3, 9D12, 12B9, 15E1, 23F11 and 26F11 are also provided. The cDNA sequences encoding the full length light chain of antibodies 1C9, 3B3, 4E1, 7A3, 9D12, 12B9, 15E1, 123F11, 26F11, 1S2, 1S3, 1S4 and 1S5, including the constant region, are set forth in SEQ ID NOs: 197, 208, 219, 230, 241, 252, 256, 260, 264, 217, 228, 239 and 250, respectively. The amino acid sequences of the full length light chain of antibodies 1C9, 3B3, 4E1, 7A3, 9D12, 12B9, 15E1, 23F11, 26F11, 1S2, 1S3, 1S4 and 1S5, including the constant region, are set forth in SEQ ID NOs: 198 (of which residues 1-20 correspond to the signal peptide and the remainder is the mature polypeptide), 209 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 220 (of which residues 1-20 correspond to the signal peptide and the remainder is the mature polypeptide), 231 (of which residues 1-20 correspond to the signal peptide and the remainder is the mature polypeptide), 242 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 253 (of which residues 1-20 correspond to the signal peptide and the remainder is the mature polypeptide), 257 (of which residues 1-20 correspond to the signal peptide and the remainder is the mature polypeptide), 261 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 265 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 218 (of which residues 1-22 correspond to the signal peptide and the remainder is the mature polypeptide), 229 (of which residues 1-22 correspond to the signal peptide and the remainder is the mature polypeptide), 240 (of which residues 1-22 correspond to the signal peptide and the remainder is the

mature polypeptide) and 251 (of which residues 1-22 correspond to the signal peptide and the remainder is the mature polypeptide), respectively.

The cDNA sequences encoding the full length heavy chain of antibodies 1C9, 3B3, 4E1, 7A3, 9D12, 12B9, 15E1, 23F11, 26F11 and 1S1, including the constant region, are set forth in SEQ ID NOs: 199, 210, 221, 232, 243, 254, 258, 262, 266 and 206, respectively. The amino acid sequences of the full length heavy chain of antibodies 1C9, 3B3, 4E1, 7A3, 9D12, 12B9, 15E1, 23F11, 26F11 and 1S1, including the constant region, are set forth in SEQ ID NOs: 200 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 211 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 222 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 233 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 244 (no signal peptide), 255 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 259 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), 263 (of which residues 1-20 correspond to the signal peptide and the remainder is the mature polypeptide), 267 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide) and 207 (of which residues 1-19 correspond to the signal peptide and the remainder is the mature polypeptide), respectively.

In some embodiments of the invention, antibodies comprise amino acids 20-467 of SEQ ID NO: 207 (1S1 heavy chain) and amino acids 21-234 of SEQ ID NO: 220 (1S1 light chain); or amino acids 20-466 of SEQ ID NO: 233 (1S2 heavy chain) and amino acids 23-234 of SEQ ID NO: 218 (1S2 light chain); or amino acids 20-466 of SEQ ID NO: 255 (1S3 heavy chain) and amino acids 23-234 of SEQ ID NO: 229 (1S3 light chain); or amino acids 20-466 of SEQ ID NO: 259 (1S4 heavy chain) and wherein amino acids 23-234 of SEQ ID NO: 240 (1S4 light chain); or amino acids 20-466 of SEQ ID NO: 267 (1S5 heavy chain) and amino acids 23-234 of SEQ ID NO: 251 (1S5 light chain).

The term "monoclonal antibody" as used herein refers to an antibody, as that term is defined herein, obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations or alternative post-translational modifications that may be present in minor amounts, whether produced from hybridomas or recombinant DNA techniques. Nonlimiting examples of monoclonal antibodies include murine, rabbit, rat, chicken, chimeric, humanized, or human antibodies, fully assembled antibodies, multispecific antibodies (including bispecific antibodies), antibody fragments that can bind an antigen (including, Fab', $F'(ab)_2$, Fv, single chain antibodies, diabodies), maxibodies, nanobodies, and recombinant peptides comprising the foregoing as long as they exhibit the desired biological activity, or variants or derivatives thereof. Humanizing or modifying antibody sequence to be more human-like is described in, e.g., Jones et al., Nature 321:522 525 (1986); Morrison et al., *Proc. Natl. Acad. Sci., U.S.A.,* 81:6851 6855 (1984); Morrison and 01, *Adv. Immunol.,* 44:65 92 (1988); Verhoeyer et al., *Science* 239:1534 1536 (1988); Padlan, *Molec. Immun.,* 28:489 498 (1991); Padlan, *Molec. Immunol.,* 31(3):169 217 (1994); and Kettleborough, C. A. et al., *Protein Engineering.,* 4(7):773 83 (1991); Co, M. S., et al. (1994), *J. Immunol.* 152, 2968-2976); Studnicka et al., *Protein Engineering* 7: 805-814 (1994); each of which is incorporated herein by reference in its entirety. One method for isolating human monoclonal antibodies is the use of phage display technology. Phage display is described in e.g., Dower et al., WO 91/17271, McCafferty et al., WO 92/01047, and Caton and Koprowski, *Proc. Natl. Acad. Sci. USA,* 87:6450-6454 (1990), each of which is incorporated herein by reference in its entirety. Another method for isolating human monoclonal antibodies uses transgenic animals that have no endogenous immunoglobulin production and are engineered to contain human immunoglobulin loci. See, e.g., Jakobovits et al., *Proc. Natl. Acad. Sci. USA,* 90:2551 (1993); Jakobovits et al., *Nature,* 362:255-258 (1993); Bruggermann et al., *Year in Immuno.,* 7:33 (1993); WO 91/10741, WO 96/34096, WO 98/24893, or U.S. Patent Application Publication Nos. 2003/0194404, 2003/0031667 or 2002/0199213; each incorporated herein by reference in its entirety.

An "isolated" antibody refers to an antibody, as that term is defined herein, that has been identified and separated from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In certain embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody, or more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or silver stain. Isolated naturally occurring antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An "immunoglobulin" or "native antibody" is a tetrameric glycoprotein. In a naturally-occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a "variable" ("V") region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Immunoglobulins can be assigned to different classes depending on the amino acid sequence of the constant domain of their heavy chains. Heavy chains are classified as mu (μ), delta (Δ), gamma (γ), alpha (α), and epsilon (ϵ), and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Several of these may be further divided into subclasses or isotypes, e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. Different isotypes have different effector functions; for example, IgG1 and IgG3 isotypes have antibody-dependent cellular cytotoxicity (ADCC) activity. Human light chains are classified as kappa (κ) and lambda (λ) light chains. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, Fundamental Immunology, Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)).

Allotypes are variations in antibody sequence, often in the constant region, that can be immunogenic and are encoded by specific alleles in humans. Allotypes have been identified for five of the human IGHC genes, the IGHG1, IGHG2, IGHG3, IGHA2 and IGHE genes, and are designated as G1m, G2m, G3m, A2m, and Em allotypes, respectively. At least 18 Gm allotypes are known: nG1m(1), nG1m(2), G1m (1, 2, 3, 17) or G1m (a, x, f, z), G2m (23) or G2m (n), G3m (5, 6, 10, 11, 13,

14, 15, 16, 21, 24, 26, 27, 28) or G3m (b1, c3, b5, b0, b3, b4, s, t, g1, c5, u, v, g5). There are two A2m allotypes A2m(1) and A2m(2).

For a detailed description of the structure and generation of antibodies, see Roth, D. B., and Craig, N. L., Cell, 94:411-414 (1998), herein incorporated by reference in its entirety. Briefly, the process for generating DNA encoding the heavy and light chain immunoglobulin sequences occurs primarily in developing B-cells. Prior to the rearranging and joining of various immunoglobulin gene segments, the V, D, J and constant (C) gene segments are found generally in relatively close proximity on a single chromosome. During B-cell-differentiation, one of each of the appropriate family members of the V, D, J (or only V and J in the case of light chain genes) gene segments are recombined to form functionally rearranged variable regions of the heavy and light immunoglobulin genes. This gene segment rearrangement process appears to be sequential. First, heavy chain D-to-J joints are made, followed by heavy chain V-to-DJ joints and light chain V-to-J joints. In addition to the rearrangement of V, D and J segments, further diversity is generated in the primary repertoire of immunoglobulin heavy and light chains by way of variable recombination at the locations where the V and J segments in the light chain are joined and where the D and J segments of the heavy chain are joined. Such variation in the light chain typically occurs within the last codon of the V gene segment and the first codon of the J segment. Similar imprecision in joining occurs on the heavy chain chromosome between the D and J_H segments and may extend over as many as 10 nucleotides. Furthermore, several nucleotides may be inserted between the D and J_H and between the V_H and D gene segments which are not encoded by genomic DNA. The addition of these nucleotides is known as N-region diversity. The net effect of such rearrangements in the variable region gene segments and the variable recombination which may occur during such joining is the production of a primary antibody repertoire.

The term "hypervariable" region refers to amino acid residues from a complementarity determining region or CDR (i.e., residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain and 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain as described by Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). Even a single CDR may recognize and bind antigen, although with a lower affinity than the entire antigen binding site containing all of the CDRs.

An alternative definition of residues from a hypervariable "loop" is described by Chothia et al., *J. Mol. Biol.,* 196: 901-917 (1987) as residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain.

"Framework" or FR residues are those variable region residues other than the hypervariable region residues.

"Antibody fragments" comprise a portion of an intact immunoglobulin, e.g., an antigen binding or variable region of the intact antibody, and include multispecific (bispecific, trispecific, etc.) antibodies formed from antibody fragments. Fragments of immunoglobulins may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies.

Nonlimiting examples of antibody fragments include Fab, Fab', $F(ab')_2$, Fv (variable region), domain antibodies (dAb, containing a VH domain) (Ward et al., *Nature,* 341:544-546, 1989), complementarity determining region (CDR) fragments, single-chain antibodies (scFv, containing VH and VL domains on a single polypeptide chain) (Bird et al., *Science,* 242:423-426, 1988, and Huston et al., *Proc. Natl. Acad. Sci., USA* 85:5879-5883, 1988, optionally including a polypeptide linker; and optionally multispecific, Gruber et al., *J. Immunol.,* 152: 5368 (1994)), single chain antibody fragments, diabodies (VH and VL domains on a single polypeptide chain that pair with complementary VL and VH domains of another chain) (EP 404,097; WO 93/11161; and Holliger et al., *Proc. Natl. Acad. Sci., USA,* 90:6444-6448 (1993)), triabodies, tetrabodies, minibodies (scFv fused to CH3 via a peptide linker (hingeless) or via an IgG hinge) (Olafsen, et al., Protein Eng Des Sel. 2004 April; 17(4):315-23), linear antibodies (tandem Fd segments (VH-CH1-VH-CH1) (Zapata et al., *Protein Eng.,* 8(10):1057-1062 (1995)); chelating recombinant antibodies (crAb, which can bind to two adjacent epitopes on the sane antigen) (Neri et al., *J Mol Biol.,* 246:367-73, 1995), bibodies (bispecific Fab-scFv) or tribodies (trispecific Fab-(scFv)(2)) (Schoonjans et al., J. Immunol. 165:7050-57, 2000; Willems et al., *J. Chromatogr. B. Analyt. Technol. Biomed. Life Sci.,* 786:161-76, 2003), intrabodies (Biocca, et al., *EMBO J.,* 9:101-108, 1990; Colby et al., *Proc. Natl. Acad. Sci. USA,* 101:17616-21, 2004) which may also comprise cell signal sequences which retain or direct the antibody intracellularly (Mhashilkar et al, EMBO J., 14:1542-51, 1995; Wheeler et al., *FASEB J.,* 17:1733-5, 2003), transbodies (cell-permeable antibodies containing a protein transduction domain (PTD) fused to scFv (Heng et al., *Med Hypotheses.,* 64:1105-8, 2005), nanobodies (approximately 15 kDa variable domain of the heavy chain) (Cortez-Retamozo et al., *Cancer Research* 64:2853-57, 2004), small modular immunopharmaceuticals (SMIPs) (U.S. Patent Application Publication 2003/0133939 and US Patent Application Publication 2003/0118592), an antigen-binding-domain immunoglobulin fusion protein, a camelized antibody (in which VH recombines with a constant region that contains hinge, CH1, CH2 and CH3 domains) (Desmyter et al., *J. Biol. Chem.,* 276: 26285-90, 2001; Ewert et al., *Biochemistry,* 41:3628-36, 2002; U.S. Patent Application Publication Nos. 2005/0136049 and 2005/0037421), a VHH containing antibody, heavy chain antibodies (HCAbs, homodimers of two heavy chains having the structure H2L2), or variants or derivatives thereof, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide, such as a CDR sequence, as long as the antibody retains the desired biological activity.

The term "variant" refers to a polypeptide sequence of an antibody that contains at least one amino acid substitution, deletion, or insertion in the variable region or the portion equivalent to the variable region, provided that the variant retains the desired binding affinity or biological activity. In addition, the antibodies as described herein may have amino acid modifications in the constant region to modify effector function of the antibody, including half-life or clearance, ADCC and/or CDC activity. Such modifications can enhance pharmacokinetics or enhance the effectiveness of the antibody in treating cancer, for example. See Shields et al., *J. Biol. Chem.,* 276(9):6591-6604 (2001), incorporated by reference herein in its entirety. In the case of IgG1, modifications to the constant region, particularly the hinge or CH2 region, may increase or decrease effector function, including ADCC and/or CDC activity. In other embodiments, an IgG2 constant region is modified to decrease antibody-antigen aggregate formation. In the case of IgG4, modifications to the constant region, particularly the hinge region, may reduce the formation of half-antibodies.

The term "modification" includes but is not limited to, one or more amino acid change (including substitutions, insertions or deletions); chemical modifications that do not inter-

fere with hepcidin-binding activity; covalent modification by conjugation to therapeutic or diagnostic agents; labeling (e.g., with radionuclides or various enzymes); covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or substitution by chemical synthesis of non-natural amino acids. In some embodiments, modified polypeptides (including antibodies) will retain the binding properties of unmodified molecules.

The term "derivative" refers to antibodies or polypeptides that are covalently modified by conjugation to therapeutic or diagnostic agents, labeling (e.g., with radionuclides or various enzymes), covalent polymer attachment such as pegylation (derivatization with polyethylene glycol) and insertion or substitution by chemical synthesis of non-natural amino acids. In some embodiments, derivatives will retain the binding properties of underivatized molecules.

Methods for making bispecific or other multispecific antibodies are known in the art and include chemical cross-linking, use of leucine zippers (Kostelny et al., *J. Immunol* 148:1547-1553, 1992); diabody technology (Hollinger et al., *Proc. Natl. Acad. Sci. USA,* 90:6444-48, 1993); scFv dimers (Gruber et al., *J. Immunol.,* 152: 5368, 1994), linear antibodies (Zapata et al., *Protein Eng.,* 8:1057-62, 1995); and chelating recombinant antibodies (Neri et al., *J. Mol. Biol.,* 246: 367-73, 1995).

Thus, a variety of compositions comprising one, two, and/or three CDRs of a heavy chain variable region or a light chain variable region of an antibody may be generated by techniques known in the art.

Recombinant Production of Antibodies

Isolated nucleic acids encoding monoclonal antibodies described herein are also provided, optionally operably linked to control sequences recognized by a host cell, vectors and host cells comprising the nucleic acids, and recombinant techniques for the production of the antibodies, which may comprise culturing the host cell so that the nucleic acid is expressed and, optionally, recovering the antibody from the host cell culture or culture medium.

Relevant amino acid sequence from an immunoglobulin of interest may be determined by direct protein sequencing, and suitable encoding nucleotide sequences can be designed according to a universal codon table. Alternatively, genomic or cDNA encoding the monoclonal antibodies may be isolated and sequenced from cells producing such antibodies using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies).

Cloning is carried out using standard techniques (see, e.g., Sambrook et al. (1989) Molecular Cloning: A Laboratory Guide, Vols 1-3, Cold Spring Harbor Press, which is incorporated herein by reference). For example, a cDNA library may be constructed by reverse transcription of polyA+ mRNA, e.g., membrane-associated mRNA, and the library screened using probes specific for human immunoglobulin polypeptide gene sequences. In one embodiment, however, the polymerase chain reaction (PCR) is used to amplify cDNAs (or portions of full-length cDNAs) encoding an immunoglobulin gene segment of interest (e.g., a light or heavy chain variable segment). The amplified sequences can be readily cloned into any suitable vector, e.g., expression vectors, minigene vectors, or phage display vectors. It will be appreciated that the particular method of cloning used is not critical, so long as it is possible to determine the sequence of some portion of the immunoglobulin polypeptide of interest.

One source for antibody nucleic acids is a hybridoma produced by obtaining a B cell from an animal immunized with the antigen of interest and fusing it to an immortal cell. Alternatively, nucleic acid can be isolated from B cells (or whole spleen) of the immunized animal. Yet another source of nucleic acids encoding antibodies is a library of such nucleic acids generated, for example, through phage display technology. Polynucleotides encoding peptides of interest, e.g., variable region peptides with desired binding characteristics, can be identified by standard techniques such as panning.

The sequence encoding an entire variable region of the immunoglobulin polypeptide may be determined; however, it will sometimes be adequate to sequence only a portion of a variable region, for example, the CDR-encoding portion. Sequencing is carried out using standard techniques (see, e.g., Sambrook et al. (1989) Molecular Cloning: A Laboratory Guide, Vols 1-3, Cold Spring Harbor Press, and Sanger, F. et al., (1977) *Proc. Natl. Acad. Sci. USA,* 74: 5463-5467, which is incorporated herein by reference). By comparing the sequence of the cloned nucleic acid with published sequences of human immunoglobulin genes and cDNAs, one of skill will readily be able to determine, depending on the region sequenced, (i) the germline segment usage of the hybridoma immunoglobulin polypeptide (including the isotype of the heavy chain) and (ii) the sequence of the heavy and light chain variable regions, including sequences resulting from N-region addition and the process of somatic mutation. One source of immunoglobulin gene sequence information is the National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Md.

As used herein, an "isolated" nucleic acid molecule or "isolated" nucleic acid sequence is a nucleic acid molecule that is either (1) identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the nucleic acid or (2) cloned, amplified, tagged, or otherwise distinguished from background nucleic acids such that the sequence of the nucleic acid of interest can be determined. An isolated nucleic acid molecule is other than in the form or setting in which it is found in nature. However, an isolated nucleic acid molecule includes a nucleic acid molecule contained in cells that ordinarily express the antibody where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

Once isolated, the DNA may be operably linked to expression control sequences or placed into expression vectors, which are then transfected into host cells that do not otherwise produce immunoglobulin protein, to direct the synthesis of monoclonal antibodies in the recombinant host cells. Recombinant production of antibodies is well known in the art.

Expression control sequences refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is operably linked when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, operably linked means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contigu-

ous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

Many vectors are known in the art. Vector components may include one or more of the following: a signal sequence (that may, for example, direct secretion of the antibody), an origin of replication, one or more selective marker genes (that may, for example, confer antibiotic or other drug resistance, complement auxotrophic deficiencies, or supply critical nutrients not available in the media), an enhancer element, a promoter, and a transcription termination sequence, all of which are well known in the art.

Cell, cell line, and cell culture are often used interchangeably and all such designations herein include progeny. Transformants and transformed cells include the primary subject cell and cultures derived therefrom without regard for the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. Mutant progeny that have the same function or biological activity as screened for in the originally transformed cell are included.

Exemplary host cells include prokaryote, yeast, or higher eukaryote cells (i.e., a multicellular organism). Prokaryotic host cells include eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *Escherichia*, e.g., *E. coli, Enterobacter, Erwinia, Klebsiella, Proteus, Salmonella*, e.g., *Salmonella typhimurium, Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as Bacilli such as *B. subtilis* and *B. licheniformis, Pseudomonas*, and *Streptomyces*. Eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for recombinant polypeptides or antibodies. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among lower eukaryotic host microorganisms. However, a number of other genera, species, and strains are commonly available and useful herein, such as *Pichia*, e.g. *P. pastoris, Schizosaccharomyces pombe; Kluyveromyces, Yarrowia; Candida; Trichoderma reesia; Neurospora crassa; Schwanniomyces* such as *Schwanniomyces occidentalis*; and filamentous fungi such as, e.g., *Neurospora, Penicillium, Tolypocladium*, and *Aspergillus* hosts such as *A. nidulans* and *A. niger.*

Host cells for the expression of glycosylated polypeptide or antibody can be derived from multicellular organisms. Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection of such cells are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV.

Vertebrate host cells are also suitable hosts, and recombinant production of polypeptide or antibody from such cells has become routine procedure. Examples of useful mammalian host cell lines are Chinese hamster ovary cells, including CHOK1 cells (ATCC CCL61), DXB-11, DG-44, and Chinese hamster ovary cells/−DHFR (CHO, Urlaub et al., *Proc. Natl. Acad. Sci. USA,* 77: 4216 (1980)); monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, [Graham et al., *J. Gen Virol.* 36: 59 (1977)]; baby hamster kidney cells (BHK, ATCC CCL 10); mouse sertoli cells (TM4, Mather, *Biol. Reprod.,* 23: 243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human hepatoma cells (Hep G2, HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., *Annals N.Y. Acad. Sci.,* 383: 44-68 (1982)); MRC 5 cells or FS4 cells; or mammalian myeloma cells.

Host cells are transformed or transfected with the above-described nucleic acids or vectors for antibody production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. In addition, novel vectors and transfected cell lines with multiple copies of transcription units separated by a selective marker are particularly useful for the expression of antibodies.

The host cells used to produce an antibody described herein may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham et al., *Meth. Enz.,* 58: 44 (1979), Barnes et al., *Anal. Biochem.,* 102: 255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Pat. Re. No. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as Gentamycin™ drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

Upon culturing the host cells, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, is removed, for example, by centrifugation or ultrafiltration.

The antibody can be purified using, for example, hydroxylapatite chromatography, cation or anion exchange chromatography, or affinity chromatography, using the antigen of interest or protein A or protein G as an affinity ligand. Protein A can be used to purify antibodies that are based on human γ1, γ2, or γ4 heavy chains (Lindmark et al., *J. Immunol. Meth.* 62: 1-13 (1983)). Protein G is recommended for all mouse isotypes and for human γ3 (Guss et al., *EMBO J.* 5: 15671575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_H3 domain, the Bakerbond ABX™resin (J. T. Baker, Phillipsburg, N.J.) is useful for purification. Other techniques for protein purification such as ethanol precipitation, Reverse Phase HPLC, chromatofocus-

ing, SDS-PAGE, and ammonium sulfate precipitation are also possible depending on the antibody to be recovered.

Chimeric and Humanized Antibodies

Because chimeric or humanized antibodies are less immunogenic in humans than the parental rodent monoclonal antibodies, they can be used for the treatment of humans with far less risk of anaphylaxis. Thus, these antibodies are contemplated in therapeutic applications that involve in vivo administration to a human.

For example, a murine antibody on repeated in vivo administration in man either alone or as a conjugate will bring about an immune response in the recipient, sometimes called a HAMA response (Human Anti Mouse Antibody). The HAMA response may limit the effectiveness of the pharmaceutical if repeated dosing is required. The immunogenicity of the antibody may be reduced by chemical modification of the antibody with a hydrophilic polymer such as polyethylene glycol or by using the methods of genetic engineering to make the antibody binding structure more human like.

The phrase "chimeric antibody," as used herein, refers to an antibody containing sequence derived from two different antibodies which typically originate from different species. Most typically, chimeric antibodies comprise variable Ig domains of a rodent monoclonal antibody fused to human constant Ig domains. Such antibodies can be generated using standard procedures known in the art (See Morrison, S. L., et al. (1984) "Chimeric Human Antibody Molecules; Mouse Antigen Binding Domains with Human Constant Region Domains," *Proc. Natl. Acad. Sci. USA,* 81, 6841-6855; and, Boulianne, G. L., et al, *Nature* 312, 643-646. (1984)). Although some chimeric monoclonal antibodies have proved less immunogenic in humans, the rodent variable Ig domains can still lead to a significant human anti-rodent response.

The phrase "humanized antibody" refers to an antibody derived from a non-human antibody, typically a rodent monoclonal antibody. Alternatively, a humanized antibody may be derived from a chimeric antibody.

Humanized antibodies may be achieved by a variety of methods including, for example: (1) grafting the non-human complementarity determining regions (CDRs) onto a human framework and constant region (a process referred to in the art as humanizing through "CDR grafting"), or, alternatively, (2) transplanting the entire non-human variable domains, but "cloaking" them with a human-like surface by replacement of surface residues (a process referred to in the art as "veneering"). These methods are disclosed in, e.g., Jones et al., Nature 321:522 525 (1986); Morrison et al., *Proc. Natl. Acad. Sci., USA,* 81:6851 6855 (1984); Morrison and Oi, *Adv. Immunol.,* 44:65 92 (1988); Verhoeyer et al., *Science* 239: 1534 1536 (1988); Padlan, *Molec. Immun.* 28:489 498 (1991); Padlan, *Molec. Immunol.* 31(3):169 217 (1994); and Kettleborough, C. A. et al., *Protein Eng.* 4(7):773 83 (1991) each of which is incorporated herein by reference in its entirety.

CDR grafting involves introducing one or more of the six CDRs from the mouse heavy and light chain variable Ig domains into the appropriate framework regions of a human variable Ig domain. This technique (Riechmann, L., et al., *Nature* 332, 323 (1988)), utilizes the conserved framework regions (FR1-FR4) as a scaffold to support the CDR loops which are the primary contacts with antigen. A significant disadvantage of CDR grafting, however, is that it can result in a humanized antibody that has a substantially lower binding affinity than the original mouse antibody, because amino acids of the framework regions can contribute to antigen binding, and because amino acids of the CDR loops can influence the association of the two variable Ig domains. To maintain the affinity of the humanized monoclonal antibody, the CDR grafting technique can be improved by choosing human framework regions that most closely resemble the framework regions of the original mouse antibody, and by site-directed mutagenesis of single amino acids within the framework or CDRs aided by computer modeling of the antigen binding site (e.g., Co, M. S., et al. (1994), *J. Immunol.* 152, 2968-2976).

One method of humanizing antibodies comprises aligning the non-human heavy and light chain sequences to human heavy and light chain sequences, selecting and replacing the non-human framework with a human framework based on such alignment, molecular modeling to predict the conformation of the humanized sequence and comparing to the conformation of the parent antibody. This process is followed by repeated back mutation of residues in the CDR region which disturb the structure of the CDRs until the predicted conformation of the humanized sequence model closely approximates the conformation of the non-human CDRs of the parent non-human antibody. Such humanized antibodies may be further derivatized to facilitate uptake and clearance, e.g., via Ashwell receptors (See, e.g., U.S. Pat. Nos. 5,530,101 and 5,585,089).

A number of humanizations of mouse monoclonal antibodies by rational design have been reported (See, for example, U.S. Patent Application Publication No. 2002/0091240 published Jul. 11, 2002, WO 92/11018 and U.S. Pat. Nos. 5,693, 762, 5,766,866).

Human Engineered™ Antibodies

The phrase "Human Engineered™ antibody" refers to an antibody derived from a non-human antibody, typically a rodent monoclonal antibody or possibly a chimeric antibody. Human Engineering™ of antibody variable domains has been described by Studnicka [See, e.g., Studnicka et al. U.S. Pat. No. 5,766,886; Studnicka et al. *Protein Engineering,* 7: 805-814 (1994)] as a method for reducing immunogenicity while maintaining binding activity of antibody molecules. According to the method, each variable region amino acid has been assigned a risk of substitution. Amino acid substitutions are distinguished by one of three risk categories: (1) low risk changes are those that have the greatest potential for reducing immunogenicity with the least chance of disrupting antigen binding; (2) moderate risk changes are those that would further reduce immunogenicity, but have a greater chance of affecting antigen binding or protein folding; (3) high risk residues are those that are important for binding or for maintaining antibody structure and carry the highest risk that antigen binding or protein folding will be affected. Due to the three-dimensional structural role of prolines, modifications at prolines are generally considered to be at least moderate risk changes, even if the position is typically a low risk position.

Variable regions of the light and heavy chains of a rodent antibody can be Human Engineered™ by substituting human amino acids at positions determined to be unlikely to adversely effect either antigen binding or protein folding, but likely to reduce immunogenicity in a human environment. Although any human variable region can be used, including an individual VH or VL sequence or a human consensus VH or VL sequence or an individual or consensus human germline sequence, generally a human sequence with highest identity or homology to the rodent sequence is used to minimize the number of substitutions. The amino acid residues at any number of the low risk positions, or at all of the low risk positions, can be changed. For example, at each low risk position where the aligned murine and human amino acid residues differ, an amino acid modification is introduced that replaces the rodent residue with the human residue. In addi-

tion, the amino acid residues at any number or all of the moderate risk positions can be changed. In some embodiments, all of the low and moderate risk positions are changed from rodent to human sequence.

Synthetic genes containing modified heavy and/or light chain variable regions are constructed and linked to human γ heavy chain and/or kappa light chain constant regions. Any human heavy chain and light chain constant regions of any class or subclass may be used in combination with the Human Engineered™ antibody variable regions.

Antibodies from Transgenic Animals Engineered to Contain Human Immunoglobulin Loci

Antibodies to hepcidin can also be produced using transgenic animals that have no endogenous immunoglobulin production and are engineered to contain human immunoglobulin loci. For example, WO 98/24893 discloses transgenic animals having a human Ig locus wherein the animals do not produce functional endogenous immunoglobulins due to the inactivation of endogenous heavy and light chain loci. Transgenic non-primate mammalian hosts capable of mounting an immune response to an immunogen, wherein the antibodies have primate constant and/or variable regions, and wherein the endogenous immunoglobulin encoding loci are substituted or inactivated have also been discussed. WO 96/30498 discloses the use of the Cre/Lox system to modify the immunoglobulin locus in a mammal, such as to replace all or a portion of the constant or variable region to form a modified antibody molecule. WO 94/02602 discloses non-human mammalian hosts having inactivated endogenous Ig loci and functional human Ig loci. U.S. Pat. No. 5,939,598 discloses methods of making transgenic mice in which the mice lack endogenous heavy chains, and express an exogenous immunoglobulin locus comprising one or more xenogeneic constant regions.

Using a transgenic animal described above, an immune response can be produced to a selected antigenic molecule, and antibody producing cells can be removed from the animal and used to produce hybridomas that secrete human-derived monoclonal antibodies. Immunization protocols, adjuvants, and the like are known in the art, and are used in immunization of, for example, a transgenic mouse as described in WO 96/33735. The monoclonal antibodies can be tested for the ability to inhibit or neutralize the biological activity or physiological effect of the corresponding protein.

See also Jakobovits et al., *Proc. Natl. Acad. Sci. USA,* 90:2551 (1993); Jakobovits et al., *Nature,* 362:255-258 (1993); Bruggermann et al., Year in Immuno., 7:33 (1993); and U.S. Pat. Nos. 5,591,669, 5,589,369, 5,545,807; and U.S. Patent Application Publication No. 2002/0199213. U.S. Patent Application Publication No. 2003/0092125 describes methods for biasing the immune response of an animal to the desired epitope. Human antibodies may also be generated by in vitro activated B cells (see U.S. Pat. Nos. 5,567,610 and 5,229,275).

Antibody Production by Phage Display Techniques

The development of technologies for making repertoires of recombinant human antibody genes, and the display of the encoded antibody fragments on the surface of filamentous bacteriophage, has provided another means for generating human-derived antibodies. Phage display is described in e.g., Dower et al., WO 91/17271, McCafferty et al., WO 92/01047, and Caton and Koprowski, *Proc. Natl. Acad. Sci. USA,* 87:6450-6454 (1990), each of which is incorporated herein by reference in its entirety. The antibodies produced by phage technology are usually produced as antigen binding fragments, e.g. Fv or Fab fragments, in bacteria and thus lack effector functions. Effector functions can be introduced by one of two strategies: The fragments can be engineered either into complete antibodies for expression in mammalian cells, or into bispecific antibody fragments with a second binding site capable of triggering an effector function.

Typically, the Fd fragment (V_H-C_H1) and light chain (V_L-C_L) of antibodies are separately cloned by PCR and recombined randomly in combinatorial phage display libraries, which can then be selected for binding to a particular antigen. The antibody fragments are expressed on the phage surface, and selection of Fv or Fab (and therefore the phage containing the DNA encoding the antibody fragment) by antigen binding is accomplished through several rounds of antigen binding and re-amplification, a procedure termed panning. Antibody fragments specific for the antigen are enriched and finally isolated.

Phage display techniques can also be used in an approach for the humanization of rodent monoclonal antibodies, called "guided selection" (see Jespers, L. S., et al., Bio/Technology 12, 899-903 (1994)). For this, the Fd fragment of the mouse monoclonal antibody can be displayed in combination with a human light chain library, and the resulting hybrid Fab library may then be selected with antigen. The mouse Fd fragment thereby provides a template to guide the selection. Subsequently, the selected human light chains are combined with a human Fd fragment library. Selection of the resulting library yields entirely human Fab.

A variety of procedures have been described for deriving human antibodies from phage-display libraries (See, for example, Hoogenboom et al., *J. Mol. Biol.,* 227:381 (1991); Marks et al., *J. Mol. Biol.,* 222:581-597 (1991); U.S. Pat. Nos. 5,565,332 and 5,573,905; Clackson, T., and Wells, J. A., *TIBTECH,* 12, 173-184 (1994)). In particular, in vitro selection and evolution of antibodies derived from phage display libraries has become a powerful tool (See Burton, D. R., and Barbas III, C. F., *Adv. Immunol.,* 57, 191-280 (1994); and, Winter, G., et al., *Annu. Rev. Immunol.,* 12, 433-455 (1994); U.S. Patent Application Publication No. 2002/0004215 and WO92/01047; U.S. Patent Application Publication No. 2003/0190317 published Oct. 9, 2003 and U.S. Pat. Nos. 6,054, 287; 5,877,293.

Watkins, "Screening of Phage-Expressed Antibody Libraries by Capture Lift," *Methods in Molecular Biology, Antibody Phage Display: Methods and Protocols,* 178: 187-193, and U.S. Patent Application Publication No. 2003/0044772 published Mar. 6, 2003 describes methods for screening phage-expressed antibody libraries or other binding molecules by capture lift, a method involving immobilization of the candidate binding molecules on a solid support.

Antibody Fragments

As noted above, antibody fragments comprise a portion of an intact full length antibody, or an antigen binding or variable region of the intact antibody, and include linear antibodies and multispecific antibodies formed from antibody fragments. Nonlimiting examples of antibody fragments include Fab, Fab', F(ab')2, Fv, Fd, domain antibody (dAb), complementarity determining region (CDR) fragments, single-chain antibodies (scFv), single chain antibody fragments, diabodies, triabodies, tetrabodies, minibodies, linear antibodies, chelating recombinant antibodies, tribodies or bibodies, intrabodies, nanobodies, small modular immunopharmaceuticals (SMIPs), an antigen-binding-domain immunoglobulin fusion protein, a camelized antibody, a VHH containing antibody, or muteins or derivatives thereof, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide, such as a CDR sequence, as long as the antibody retains the desired biological activity. Such antigen fragments may be

produced by the modification of whole antibodies or synthesized de novo using recombinant DNA technologies or peptide synthesis.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (VH) connected to a light-chain variable domain (VL) in the same polypeptide chain (VH VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., *Proc. Natl. Acad. Sci. USA,* 90:6444-6448 (1993).

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain, and optionally comprising a polypeptide linker between the V_H and V_L domains that enables the Fv to form the desired structure for antigen binding (Bird et al., *Science* 242:423-426, 1988, and Huston et al., *Proc. Natl. Acad. Sci. USA* 85:5879-5883, 1988). An Fd fragment consists of the V_H and C_H1 domains.

Additional antibody fragments include a domain antibody (dAb) fragment (Ward et al., *Nature* 341:544-546, 1989) which consists of a V_H domain.

"Linear antibodies" comprise a pair of tandem Fd segments (V_H-C_H1-V_H-C_H1) which form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific (Zapata et al., *Protein Eng.,* 8:1057-62 (1995)).

A "minibody" consisting of scFv fused to CH3 via a peptide linker (hingeless) or via an IgG hinge has been described in Olafsen, et al., *Protein Eng. Des. Sel.,* 2004 April; 17(4): 315-23.

The term "maxibody" refers to bivalent scFvs covalently attached to the Fc region of an immunoglobulin, see, for example, Fredericks et al, *Protein Engineering, Design & Selection,* 17:95-106 (2004) and Powers et al., *Journal of Immunological Methods,* 251:123-135 (2001).

Functional heavy-chain antibodies devoid of light chains are naturally occurring in certain species of animals, such as nurse sharks, wobbegong sharks and Camelidae, such as camels, dromedaries, alpacas and llamas. The antigen-binding site is reduced to a single domain, the VH_H domain, in these animals. These antibodies form antigen-binding regions using only heavy chain variable region, i.e., these functional antibodies are homodimers of heavy chains only having the structure H_2L_2 (referred to as "heavy-chain antibodies" or "HCAbs"). Camelized V_{HH} reportedly recombines with IgG2 and IgG3 constant regions that contain hinge, CH2, and CH3 domains and lack a CH1 domain. Classical V_H-only fragments are difficult to produce in soluble form, but improvements in solubility and specific binding can be obtained when framework residues are altered to be more VH_H-like. (See, e.g., Reichman, et al., *J. Immunol. Methods,* 1999, 231:25-38.) Camelized V_{HH} domains have been found to bind to antigen with high affinity (Desmyter et al., *J. Biol. Chem.* 276:26285-90, 2001) and possess high stability in solution (Ewert et al., *Biochemistry* 41:3628-36, 2002). Methods for generating antibodies having camelized heavy chains are described in, for example, in U.S. Patent Application Publication Nos. 2005/0136049 and 2005/0037421. Alternative scaffolds can be made from human variable-like domains that more closely match the shark V-NAR scaffold and may provide a framework for a long penetrating loop structure.

Because the variable domain of the heavy-chain antibodies is the smallest fully functional antigen-binding fragment with a molecular mass of only 15 kDa, this entity is referred to as a nanobody (Cortez-Retamozo et al., Cancer Research 64:2853-57, 2004). A nanobody library may be generated from an immunized dromedary as described in Conrath et al., (*Antimicrob Agents Chemother,* 45: 2807-12, 2001).

Intrabodies are single chain antibodies which demonstrate intracellular expression and can manipulate intracellular protein function (Biocca, et al., EMBO J. 9:101-108, 1990; Colby et al., *Proc Natl Acad Sci USA.* 101:17616-21, 2004). Intrabodies, which comprise cell signal sequences which retain the antibody contruct in intracellular regions, may be produced as described in Mhashilkar et al (*EMBO J* 14:1542-51, 1995) and Wheeler et al. (*FASEB J.* 17:1733-5. 2003). Transbodies are cell-permeable antibodies in which a protein transduction domains (PTD) is fused with single chain variable fragment (scFv) antibodies Heng et al., (*Med Hypotheses.,* 64:1105-8, 2005).

Further contemplated are antibodies that are SMIPs or binding domain immunoglobulin fusion proteins specific for target protein. These constructs are single-chain polypeptides comprising antigen binding domains fused to immunoglobulin domains necessary to carry out antibody effector functions. See e.g., WO03/041600, U.S. Patent Application Publication No. 2003/0133939 and US Patent Application Publication No. 2003/0118592.

Multivalent Antibodies

In some embodiments, it may be desirable to generate multivalent or even a multispecific (e.g. bispecific, trispecific, etc.) monoclonal antibody. Such antibody may have binding specificities for at least two different epitopes of the target antigen, or alternatively it may bind to two different molecules, e.g. to the target antigen and to a cell surface protein or receptor. For example, a bispecific antibody may include an arm that binds to the target and another arm that binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g., CD2 or CD3), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the target-expressing cell. As another example, bispecific antibodies may be used to localize cytotoxic agents to cells which express target antigen. These antibodies possess a target-binding arm and an arm which binds the cytotoxic agent (e.g., saporin, anti-interferon-60, vinca alkaloid, ricin A chain, methotrexate or radioactive isotope hapten). Multispecific antibodies can be prepared as full length antibodies or antibody fragments.

Additionally, the anti-hepcidin antibodies disclosed herein can also be constructed to fold into multivalent forms, which may improve binding affinity, specificity and/or increased half-life in blood. Multivalent forms of anti-hepcidin antibodies can be prepared by techniques known in the art.

Bispecific or multispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Pat. No. 4,676,980, along with a number of cross-linking techniques. Another method is designed to make tetramers by adding a streptavidin-coding sequence at the C-terminus of the scFv. Streptavidin is composed of four subunits, so when the scFv-streptavidin is folded, four subunits associate to form a tetramer (Kipriyanov et al., Hum Antibodies Hybridomas 6(3): 93-101 (1995), the disclosure of which is incorporated herein by reference in its entirety).

According to another approach for making bispecific antibodies, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell cul-

ture. One interface comprises at least a part of the C_H3 domain of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g., tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g., alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers. See WO 96/27011 published Sep. 6, 1996.

Techniques for generating bispecific or multispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific or trispecific antibodies can be prepared using chemical linkage. Brennan et al., *Science* 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes. Better et al., *Science* 240: 1041-1043 (1988) disclose secretion of functional antibody fragments from bacteria (see, e.g., Better et al., Skerra et al. Science 240: 1038-1041 (1988)). For example, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form bispecific antibodies (Carter et al., *Bio/Technology* 10:163-167 (1992); Shalaby et al., *J. Exp. Med.,* 175:217-225 (1992)).

Shalaby et al., *J. Exp. Med.,* 175:217-225 (1992) describe the production of a fully humanized bispecific antibody $F(ab')_2$ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling in vitro to form the bispecfic antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the HER2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific or multispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers, e.g. GCN4. (See generally Kostelny et al., *J. Immunol.* 148(5): 1547-1553 (1992).) The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers.

Diabodies, described above, are one example of a bispecific antibody. See, for example, Hollinger et al., *Proc. Natl. Acad. Sci. USA,* 90:6444-6448 (1993). Bivalent diabodies can be stabilized by disulfide linkage.

Stable monospecific or bispecific Fv tetramers can also be generated by noncovalent association in $(scFv_2)_2$ configuration or as bis-tetrabodies. Alternatively, two different scFvs can be joined in tandem to form a bis-scFv.

Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber et al., *J. Immunol.* 152: 5368 (1994). One approach has been to link two scFv antibodies with linkers or disulfide bonds (Mallender and Voss, *J. Biol. Chem.,* 269:199-2061994, WO 94/13806, and U.S. Pat. No. 5,989,830, the disclosures of which are incorporated herein by reference in their entireties).

Alternatively, the bispecific antibody may be a "linear antibody" produced as described in Zapata et al. *Protein Eng.* 8(10):1057-1062 (1995). Briefly, these antibodies comprise a pair of tandem Fd segments (V_H-C_H1-V_H-C_H1) which form a pair of antigen binding regions. Linear antibodies can be bispecific or monospecific.

Antibodies with more than two valencies are also contemplated. For example, trispecific antibodies can be prepared. (Tutt et al., *J. Immunol* 147:60 (1991)).

A "chelating recombinant antibody" is a bispecific antibody that recognizes adjacent and non-overlapping epitopes of the target antigen, and is flexible enough to bind to both epitopes simultaneously (Neri et al., *J Mol Biol.* 246:367-73, 1995).

Production of bispecific Fab-scFv ("bibody") and trispecific Fab-(scFv)(2) ("tribody") are described in Schoonjans et al. (*J Immunol.* 165:7050-57, 2000) and Willems et al. (*J Chromatogr B Analyt Technol Biomed Life Sci.* 786:161-76, 2003). For bibodies or tribodies, a scFv molecule is fused to one or both of the VL-CL (L) and VH-CH_1 (Fd) chains, e.g., to produce a tribody two scFvs are fused to C-term of Fab while in a bibody one scFv is fused to C-term of Fab.

In yet another method, dimers, trimers, and tetramers are produced after a free cysteine is introduced in the parental protein. A peptide-based cross linker with variable numbers (two to four) of maleimide groups was used to cross link the protein of interest to the free cysteines (Cochran et al., Immunity 12(3): 241-50 (2000), the disclosure of which is incorporated herein in its entirety).

Specific Binding Agents

Other hepcidin-specific binding agents can be prepared, for example, based on CDRs from an antibody or by screening libraries of diverse peptides or organic chemical compounds for peptides or compounds that exhibit the desired binding properties for human hepcidin. Hepcidin specific binding agent include peptides containing amino acid sequences that are at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to one or more CDRs of murine antibody Ab43 (SEQ ID NOs: 16-21); murine antibody 2.7 (SEQ ID NOs: 28-33); murine antibody 2.41 (SEQ ID NOs: 40-45), rat antibody R9 (SEQ ID NOs: 52-57) or human antibody 1C9 (SEQ ID NOs: 111-116), human antibody 3B3 (SEQ ID NOs: 121-126), human antibody 4E1 (SEQ ID NOs: 131-136), human antibody 7A3 (SEQ ID NOs: 141-46), human antibody 9D12 (SEQ ID NOs: 151-156), human antibody 12B9 (SEQ ID NOs: 161-166), human antibody 15E1 (SEQ ID NOs: 171-176), human antibody 18B11 (SEQ ID NOs: 334-339), human antibody 18D8 (SEQ ID NOs: 314-319), human antibody 19B8 (SEQ ID NOs: 343-349), human antibody 19C1 (SEQ ID NOs: 324-329), human antibody 19D12 (SEQ ID NOs: 294-299), human antibody 19H6 (SEQ ID NOs: 304-309), human antibody 20E12 (SEQ ID NOs: 353-359), human antibody 22F12 (SEQ ID NOs: 363-369), human antibody 22H10 (SEQ ID NOs: 373-379), human antibody 23A11 (SEQ ID NOs: 383-389), human antibody 23F11 (SEQ ID NOs: 181-186), human antibody 24E4 (SEQ ID NOs: 393-399), human antibody 26F11 (SEQ ID NOs: 191-196), or human antibody 1S1 (SEQ ID NOs: 203-205 and 131-133) or human antibody 1S2 (SEQ ID NOs: 214-216 and 144-146) or human antibody 1S3 (SEQ ID NOs:

225-227 and 164-166) or human antibody 1S4 (SEQ ID NOs: 236-238 and 174-176) or human antibody 1S5 (SEQ ID NO: 247-249 and 184-186.

Hepcidin-specific binding agents also include peptibodies. The term "peptibody" refers to a molecule comprising an antibody Fc domain attached to at least one peptide. The production of peptibodies is generally described in PCT publication WO 00/24782, published May 4, 2000. Any of these peptides may be linked in tandem (i.e., sequentially), with or without linkers. Peptides containing a cysteinyl residue may be cross-linked with another Cys-containing peptide, either or both of which may be linked to a vehicle. Any peptide having more than one Cys residue may form an intrapeptide disulfide bond, as well. Any of these peptides may be derivatized, for example, the carboxyl terminus may be capped with an amino group, cysteines may be cappe, or amino acid residues may substituted by moieties other than amino acid residues (see, e.g., Bhatnagar et al., *J. Med. Chem.,* 39: 3814-9 (1996), and Cuthbertson et al., *J. Med. Chem.,* 40: 2876-82 (1997), which are incorporated by reference herein in their entirety). The peptide sequences may be optimized, analogous to affinity maturation for antibodies, or otherwise altered by alanine scanning or random or directed mutagenesis followed by screening to identify the best binders. Lowman, *Ann. Rev. Biophys. Biomol. Struct.,* 26: 401-24 (1997). Various molecules can be inserted into the specific binding agent structure, e.g., within the peptide portion itself or between the peptide and vehicle portions of the specific binding agents, while retaining the desired activity of specific binding agent. One can readily insert, for example, molecules such as an Fc domain or fragment thereof, polyethylene glycol or other related molecules such as dextran, a fatty acid, a lipid, a cholesterol group, a small carbohydrate, a peptide, a detectable moiety as described herein (including fluorescent agents, radiolabels such as radioisotopes), an oligosaccharide, oligonucleotide, a polynucleotide, interference (or other) RNA, enzymes, hormones, or the like. Other molecules suitable for insertion in this fashion will be appreciated by those skilled in the art, and are encompassed within the scope of the invention. This includes insertion of for example, a desired molecule in between two consecutive amino acids, optionally joined by a suitable linker.

The development of hepcidin peptibodies is also contemplated. The interaction of a protein ligand with its receptor often takes place at a relatively large interface. However, as demonstrated for human growth hormone and its receptor, only a few key residues at the interface contribute to most of the binding energy. Clackson et al., *Science* 267: 383-6 (1995). The bulk of the protein ligand merely displays the binding epitopes in the right topology or serves functions unrelated to binding. Thus, molecules of only "peptide" length (generally 2 to 40 amino acids) can bind to the receptor protein of a given large protein ligand. Such peptides may mimic the bioactivity of the large protein ligand ("peptide agonists") or, through competitive binding, inhibit the bioactivity of the large protein ligand ("peptide antagonists").

Phage display technology has emerged as a powerful method in identifying such peptide agonists and antagonists. See, for example, Scott et al. *Science,* 249: 386 (1990); Devlin et al., *Science* 249: 404 (1990); U.S. Pat. No. 5,223,409, issued Jun. 29, 1993; U.S. Pat. No. 5,733,731, issued Mar. 31, 1998; U.S. Pat. No. 5,498,530, issued Mar. 12, 1996; U.S. Pat. No. 5,432,018, issued Jul. 11, 1995; U.S. Pat. No. 5,338,665, issued Aug. 16, 1994; U.S. Pat. No. 5,922,545, issued Jul. 13, 1999; WO 96/40987, published Dec. 19, 1996; and WO 98/15833, published Apr. 16, 1998 (each of which is incorporated by reference in its entirety). In peptide phage display libraries, random peptide sequences can be displayed by fusion with coat proteins of filamentous phage. The displayed peptides can be affinity-eluted against an antibody-immobilized extracellular domain of a receptor, if desired. The retained phage may be enriched by successive rounds of affinity purification and repropagation. The best binding peptides may be sequenced to identify key residues within one or more structurally related families of peptides. See, e.g., Cwirla et al., *Science* 276: 1696-9 (1997), in which two distinct families were identified. The peptide sequences may also suggest which residues may be safely replaced by alanine scanning or by mutagenesis at the DNA level. Mutagenesis libraries may be created and screened to further optimize the sequence of the best binders. Lowman, *Ann. Rev. Biophys. Biomol. Struct.,* 26: 401-24 (1997).

Structural analysis of protein-protein interaction may also be used to suggest peptides that mimic the binding activity of large protein ligands. In such an analysis, the crystal structure may suggest the identity and relative orientation of critical residues of the large protein ligand, from which a peptide may be designed. See, e.g., Takasaki et al., *Nature Biotech* 15: 1266-70 (1997). These analytical methods may also be used to investigate the interaction between a receptor protein and peptides selected by phage display, which may suggest further modification of the peptides to increase binding affinity.

Other methods compete with phage display in peptide research. A peptide library can be fused to the carboxyl terminus of the lac repressor and expressed in *E. coli*. Another *E. coli*-based method allows display on the cell's outer membrane by fusion with a peptidoglycan-associated lipoprotein (PAL). Hereinafter, these and related methods are collectively referred to as "*E. coli* display." In another method, translation of random RNA is halted prior to ribosome release, resulting in a library of polypeptides with their associated RNA still attached. Hereinafter, this and related methods are collectively referred to as "ribosome display." Other methods employ chemical linkage of peptides to RNA. See, for example, Roberts and Szostak, *Proc. Natl. Acad. Sci. USA,* 94: 12297-303 (1997). Hereinafter, this and related methods are collectively referred to as "RNA-peptide screening." Chemically derived peptide libraries have been developed in which peptides are immobilized on stable, non-biological materials, such as polyethylene rods or solvent-permeable resins. Another chemically derived peptide library uses photolithography to scan peptides immobilized on glass slides. Hereinafter, these and related methods are collectively referred to as "chemical-peptide screening." Chemical-peptide screening may be advantageous in that it allows use of D-amino acids and other unnatural analogues, as well as non-peptide elements. Both biological and chemical methods are reviewed in Wells and Lowman, *Curr. Opin. Biotechnol.,* 3: 355-62 (1992).

Conceptually, one may discover peptide mimetics of any protein using phage display and the other methods mentioned above. These methods have been used for epitope mapping, for identification of critical amino acids in protein-protein interactions, and as leads for the discovery of new therapeutic agents. See, e.g., Cortese et al., *Curr. Opin. Biotech.,* 7: 616-21 (1996). Peptide libraries are now being used most often in immunological studies, such as epitope mapping. See Kreeger, *The Scientist,* 10(13):19-20 (1996).

Sources for compounds that may be screened for ability to bind to or modulate (i.e., increase or decrease) the activity of the hepcidin polypeptides described herein include (1) inorganic and organic chemical libraries, (2) natural product

libraries, and (3) combinatorial libraries comprised of either random or mimetic peptides, oligonucleotides or organic molecules.

Chemical libraries may be readily synthesized or purchased from a number of commercial sources, and may include structural analogs of known compounds or compounds that are identified as "hits" or "leads" via natural product screening.

The sources of natural product libraries are microorganisms (including bacteria and fungi), animals, plants or other vegetation, or marine organisms, and libraries of mixtures for screening may be created by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of the organisms themselves. Natural product libraries include polyketides, non-ribosomal peptides, and (non-naturally occurring) variants thereof. For a review, see *Science* 282:63-68 (1998).

Combinatorial libraries are composed of large numbers of peptides, oligonucleotides or organic compounds and can be readily prepared by traditional automated synthesis methods, PCR, cloning or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, *Curr. Opin. Biotechnol.* 8:701-707 (1997). For reviews and examples of peptidomimetic libraries, see Al-Obeidi et al., *Mol. Biotechnol.,* 9(3):205-23 (1998); Hruby et al., *Curr. Opin. Chem. Biol.,* 1(1):114-19 (1997); Dorner et al., *Bioorg. Med. Chem.,* 4(5):709-15 (1996) (alkylated dipeptides).

Hepcidin-specific binding agents also include scaffolding proteins, as described by Hays et al. *Trends In Biotechnology,* 23(10):514-522 (2005), herein incorporated by reference in its entirety, and Avimer protein technology, as described in U.S. Publication Nos. 2006-0286603 and 2006-0223114, both herein incorporated by reference in their entireties.

Screening Methods for Antibodies or Specific Binding Agents

Methods of identifying antibodies or specific binding agents which bind hepcidin and/or which cross-block exemplary antibodies described herein, and/or which inhibit hepcidin activity are also provided.

Antibodies or specific binding agents may be screened for binding affinity by methods known in the art. For example, gel-shift assays, Western blots, radiolabeled competition assay, co-fractionation by chromatography, co-precipitation, cross linking, ELISA, and the like may be used, which are described in, for example, Current Protocols in Molecular Biology (1999) John Wiley & Sons, NY, which is incorporated herein by reference in its entirety.

To initially screen for antibodies or specific binding agents which bind to the desired epitope on the target antigen, a routine cross-blocking assay such as that described in Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. Routine competitive binding assays may also be used, in which the unknown antibody is characterized by its ability to inhibit binding of target to a target-specific antibody described herein. Intact antigen, fragments thereof such as the extracellular domain, or linear epitopes can be used. Epitope mapping is described in Champe et al., *J. Biol. Chem.* 270: 1388-1394 (1995). Competitive binding assays may also be used to determine the off-rate of an antibody-antigen interaction. For example, one example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., ^{3}H or ^{125}I), or fragment or variant thereof, with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The binding off-rates can be determined from the data by scatchard plot analysis.

In one variation of an in vitro binding assay, method is provided comprising (a) contacting an immobilized hepcidin with a candidate antibody or specific binding agent and (b) detecting binding of the candidate antibody or specific binding agent to the hepcidin. In an alternative embodiment, the candidate antibody or specific binding agent is immobilized and binding of hepcidin is detected. Immobilization is accomplished using any of the methods well known in the art, including covalent bonding to a support, a bead, or a chromatographic resin, as well as non-covalent, high affinity interaction such as antibody binding, or use of streptavidin/biotin binding wherein the immobilized compound includes a biotin moiety. Detection of binding can be accomplished (i) using a radioactive label on the compound that is not immobilized, (ii) using a fluorescent label on the non-immobilized compound, (iii) using an antibody immunospecific for the non-immobilized compound, (iv) using a label on the non-immobilized compound that excites a fluorescent support to which the immobilized compound is attached, as well as other techniques well known and routinely practiced in the art.

In some embodiments, antibodies or specific binding agents that inhibit or neutralize human hepcidin activity may be identified by contacting hepcidin with the antibody (or specific binding agent), comparing hepcidin activity in the presence and absence of the test antibody (or specific binding agent), and determining whether the presence of the antibody (or specific binding agent) decreases activity of the hepcidin. The biological activity of a particular antibody, or specific binding agent, or combination of antibodies or specific binding agents, may be evaluated in vivo using a suitable animal model, including any of those described herein.

In some embodiments, high throughput screening (HTS) assays to identify antibodies that interact with or inhibit biological activity (i.e., inhibit phosphorylation, dimerization, ligand induced-receptor activation, or intracellular signaling, etc.) of target antigen are also contemplated. HTS assays permit screening of large numbers of compounds in an efficient manner. Cell-based HTS systems are contemplated to investigate the interaction between target antigen and its binding partners. HTS assays are designed to identify "hits" or "lead compounds" having the desired property, from which modifications can be designed to improve the desired property.

In another embodiment, high throughput screening for antibody fragments or CDRs with 1, 2, 3 or more modifications to amino acids within the CDRs having suitable binding affinity to a target antigen polypeptide is employed.

Production of Antibody Variants and Derivatives

The anti-hepcidin antibodies disclosed herein can readily be modified by techniques well-known to one of ordinary skill in the art. Potential mutations include insertion, deletion or substitution of one or more residues. In some embodiment, insertions or deletions are in the range of about 1 to 5 amino acids, in the range of about 1 to 3 amino acids, or in the range of about 1 or 2 amino acids.

Deletion variants are polypeptides wherein at least one amino acid residue of any amino acid sequence is removed. Deletions can be effected at one or both termini of the protein, or with removal of one or more residues within (i.e., internal to) the polypeptide. Methods for preparation of deletion variants are routine in the art. See, e.g., Sambrook et al. (1989) Molecular Cloning: A Laboratory Guide, Vols 1-3, Cold

Spring Harbor Press, the disclosure of which is incorporated herein by reference in its entirety.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing hundreds or more residues, as well as internal sequence insertions of one or more amino acids. As with any of the different variant types described herein, insertional variants can be designed such that the resulting polypeptide retains the same biological properties or exhibits a new physical, chemical and/or biological property not associated with the parental polypeptide from which it was derived. Methods for preparation of insertion variants are also routine and well known in the art (Sambrook et al., supra).

Fusion proteins comprising a polypeptide comprising an anti-hepcidin antibody described herein, and a heterologous polypeptide, are a specific type of insertion variant contemplated herein. Nonlimiting examples of heterologous polypeptides which can be fused to polypeptides of interest include proteins with long circulating half-life, such as, but not limited to, immunoglobulin constant regions (e.g., Fc region); marker sequences that permit identification of the polypeptide of interest; sequences that facilitate purification of the polypeptide of interest; and sequences that promote formation of multimeric proteins.

Methods of making antibody fusion proteins are well known in the art. See, e.g., U.S. Pat. No. 6,306,393, the disclosure of which is incorporated herein by reference in its entirety. In certain embodiments, fusion proteins are produced which may include a flexible linker, which connects the chimeric scFv antibody to the heterologous protein moiety. Appropriate linker sequences are those that do not affect the ability of the resulting fusion protein to be recognized and bind the epitope specifically bound by the V domain of the protein (see, e.g., WO 98/25965, the disclosure of which is incorporated herein by reference in its entirety).

Substitution variants are those in which at least one residue in the polypeptide amino acid sequence is removed and a different residue is inserted in its place. Modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. In certain embodiments, substitution variants are designed, i.e., one or more specific (as opposed to random) amino acid residues are substituted with a specific amino acid residue. Typical changes of these types include conservative substitutions and/or substitution of one residue for another based on similar properties of the native and substituting residues.

Conservative substitutions are shown in Table 1. The most conservative substitution is found under the heading of "preferred substitutions." If such substitutions result in no change in biological activity, then more substantial changes may be introduced and the products screened.

TABLE 1

Original	Exemplary	Preferred Residue Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; asp, lys; gln	arg
Asp (D)	glu; asn	glu
Cys (C)	ser; ala	ser
Gln (Q)	asn; glu	asn
Glu (E)	asp; gln	asp
Gly (G)	ala	
His (H)	asn; gln; lys; arg	
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	
Pro (P)	ala	
Ser (S)	thr	
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

Amino acid residues which share common side-chain properties are often grouped as follows.

(1) hydrophobic: norleucine, met, ala, val, leu, ile;

(2) neutral hydrophilic: cys, ser, thr;

(3) acidic: asp, glu;

(4) basic: asn, gln, his, lys, arg;

(5) residues that influence chain orientation: gly, pro; and

(6) aromatic: trp, tyr, phe.

Antibody Variants

In certain instances, antibody variants are prepared with the intent to modify those amino acid residues which are directly involved in epitope binding. In other embodiments, modification of residues which are not directly involved in epitope binding or residues not involved in epitope binding in any way, is desirable, for purposes discussed herein. Mutagenesis within any of the CDR regions and/or framework regions is contemplated.

In order to determine which antibody amino acid residues are important for epitope recognition and binding, alanine scanning mutagenesis can be performed to produce substitution variants. See, for example, Cunningham et al., *Science,* 244:1081-1085 (1989), the disclosure of which is incorporated herein by reference in its entirety. In this method, individual amino acid residues are replaced one-at-a-time with an alanine residue and the resulting anti-hepcidin antibody is screened for its ability to bind its specific epitope relative to the unmodified antibody. Modified antibodies with reduced binding capacity are sequenced to determine which residue was changed, indicating its significance in binding or biological properties.

Substitution variants of antibodies can be prepared by affinity maturation wherein random amino acid changes are introduced into the parent antibody sequence. See, for example, Ouwehand et al., Vox Sang 74 (Suppl 2):223-232, 1998; Rader et al., *Proc. Natl. Acad. Sci. USA* 95:8910-8915, 1998; Dall'Acqua et al., *Curr. Opin. Struct. Biol.,* 8:443-450, 1998, the disclosures of which are incorporated herein by reference in their entireties. Affinity maturation involves preparing and screening the anti-hepcidin antibodies, or variants thereof and selecting from the resulting variants those that have modified biological properties, such as increased binding affinity relative to the parent anti-hepcidin antibody. A convenient way for generating substitutional variants is affinity maturation using phage display. Briefly, several hypervariable region sites are mutated to generate all possible amino substitutions at each site. The variants thus generated are expressed in a monovalent fashion on the surface of filamentous phage particles as fusions to the gene III product of M13

packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity). See e.g., WO 92/01047, WO 93/112366, WO 95/15388 and WO 93/19172.

Current antibody affinity maturation methods belong to two mutagenesis categories: stochastic and nonstochastic. Error prone PCR, mutator bacterial strains (Low et al., *J. Mol. Biol.* 260, 359-68, 1996), and saturation mutagenesis (Nishimiya et al., *J. Biol. Chem.* 275:12813-20, 2000; Chowdhury, P. S. *Methods Mol. Biol.* 178, 269-85, 2002) are typical examples of stochastic mutagenesis methods (Rajpal et al., *Proc Natl Acad Sci USA.* 102:8466-71, 2005). Nonstochastic techniques often use alanine-scanning or site-directed mutagenesis to generate limited collections of specific muteins. Some methods are described in further detail below.

Affinity maturation via panning methods—Affinity maturation of recombinant antibodies is commonly performed through several rounds of panning of candidate antibodies in the presence of decreasing amounts of antigen. Decreasing the amount of antigen per round selects the antibodies with the highest affinity to the antigen thereby yielding antibodies of high affinity from a large pool of starting material. Affinity maturation via panning is well known in the art and is described, for example, in Huls et al. (*Cancer Immunol Immunother.* 50:163-71, 2001). Methods of affinity maturation using phage display technologies are described elsewhere herein and known in the art (see e.g., Daugherty et al., *Proc Natl Acad Sci USA.* 97:2029-34, 2000).

Look-through mutagenesis—Look-through mutagenesis (LTM) (Rajpal et al., *Proc Natl Acad Sci USA.* 102:8466-71, 2005) provides a method for rapidly mapping the antibody-binding site. For L™, nine amino acids, representative of the major side-chain chemistries provided by the 20 natural amino acids, are selected to dissect the functional side-chain contributions to binding at every position in all six CDRs of an antibody. LTM generates a positional series of single mutations within a CDR where each "wild type" residue is systematically substituted by one of nine selected amino acids. Mutated CDRs are combined to generate combinatorial single-chain variable fragment (scFv) libraries of increasing complexity and size without becoming prohibitive to the quantitative display of all muteins. After positive selection, clones with improved binding are sequenced, and beneficial mutations are mapped.

Error prone PCR—Error-prone PCR involves the randomization of nucleic acids between different selection rounds. The randomization occurs at a low rate by the intrinsic error rate of the polymerase used but can be enhanced by error-prone PCR (Zaccolo et al., J. Mol. Biol. 285:775-783, 1999) using a polymerase having a high intrinsic error rate during transcription (Hawkins et al., J Mol. Biol. 226:889-96, 1992). After the mutation cycles, clones with improved affinity for the antigen are selected using routine methods in the art.

Techniques utilizing gene shuffling and directed evolution may also be used to prepare and screen anti-hepcidin antibodies, or variants thereof, for desired activity. For example, Jermutus et al., Proc Natl Acad Sci USA., 98(1):75-80 (2001) showed that tailored in vitro selection strategies based on ribosome display were combined with in vitro diversification by DNA shuffling to evolve either the off-rate or thermodynamic stability of scFvs; Fermer et al., Tumour Biol. 2004 January-April; 25(1-2):7-13 reported that use of phage display in combination with DNA shuffling raised affinity by almost three orders of magnitude. Dougherty et al., Proc Natl Acad Sci USA. 2000 Feb. 29; 97(5):2029-2034 reported that (i) functional clones occur at an unexpectedly high frequency in hypermutated libraries, (ii) gain-of-function mutants are well represented in such libraries, and (iii) the majority of the scFv mutations leading to higher affinity correspond to residues distant from the binding site.

Alternatively, or in addition, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and antigen, or to use computer software to model such contact points. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, they are subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Antibody with Modified Carbohydrate

Antibody variants can also be produced that have a modified glycosylation pattern relative to the parent antibody, for example, adding or deleting one or more of the carbohydrate moieties bound to the specific binding agent or antibody, and/or adding or deleting one or more glycosylation sites in the specific binding agent or antibody.

Glycosylation of polypeptides, including antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. The presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. Thus, N-linked glycosylation sites may be added to a specific binding agent or antibody by altering the amino acid sequence such that it contains one or more of these tripeptide sequences. O-linked glycosylation refers to the attachment of one of the sugars N-aceylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used. O-linked glycosylation sites may be added to a specific binding agent or antibody by inserting or substituting one or more serine or threonine residues to the sequence of the original specific binding agent or antibody.

Altered Effector Function

Cysteine residue(s) may be removed or introduced in the Fc region of an antibody or Fc-containing polypeptide, thereby eliminating or increasing interchain disulfide bond formation in this region. A homodimeric specific binding agent or antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., *J. Exp. Med.,* 176:1191-1195 (1992) and Shopes, B., *J. Immunol.* 148: 2918-2922 (1992). Homodimeric specific binding agents or antibodies may also be prepared using heterobifunctional cross-linkers as described in Wolff et al., *Cancer Research,* 53:2560-2565 (1993). Alternatively, a specific binding agent or antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., *Anti-Cancer Drug Design* 3:219-230 (1989).

It has been shown that sequences within the CDR can cause an antibody to bind to MHC Class II and trigger an unwanted helper T-cell response. A conservative substitution can allow the specific binding agent or antibody to retain binding activity yet reduce its ability to trigger an unwanted T-cell response. It is also contemplated that one or more of the N-terminal 20 amino acids of the heavy or light chain are removed.

In some embodiments, production of antibody molecules are contemplated with altered carbohydrate structure result-

ing in altered effector activity, including antibody molecules with absent or reduced fucosylation that exhibit improved ADCC activity. A variety of ways are known in the art to accomplish this. For example, ADCC effector activity is mediated by binding of the antibody molecule to the FcγRIII receptor, which has been shown to be dependent on the carbohydrate structure of the N-linked glycosylation at the Asn-297 of the CH2 domain. Non-fucosylated antibodies bind this receptor with increased affinity and trigger FcγRIII-mediated effector functions more efficiently than native, fucosylated antibodies. For example, recombinant production of non-fucosylated antibody in CHO cells in which the alpha-1,6-fucosyl transferase enzyme has been knocked out results in antibody with 100-fold increased ADCC activity (Yamane-Ohnuki et al., Biotechnol Bioeng. 2004 Sep. 5; 87(5):614-22). Similar effects can be accomplished through decreasing the activity of this or other enzymes in the fucosylation pathway, e.g., through siRNA or antisense RNA treatment, engineering cell lines to knockout the enzyme(s), or culturing with selective glycosylation inhibitors (Rothman et al., Mol. Immunol. 1989 December; 26(12):1113-23). Some host cell strains, e.g. Lec13 or rat hybridoma YB2/0 cell line naturally produce antibodies with lower fucosylation levels. Shields et al., J Biol. Chem. 2002 Jul. 26; 277(30):26733-40; Shinkawa et al., J Biol. Chem. 2003 Jan. 31; 278(5):3466-73. An increase in the level of bisected carbohydrate, e.g. through recombinantly producing antibody in cells that overexpress GnTIII enzyme, has also been determined to increase ADCC activity. Umana et al., Nat. Biotechnol. 1999 February; 17(2): 176-80. It has been predicted that the absence of only one of the two fucose residues may be sufficient to increase ADCC activity. (Ferrara et al., J Biol. Chem. 2005 Dec. 5).

Other Covalent Modifications

Covalent modifications of a polypeptide, or antibody are also included within the scope of this invention. They may be made by chemical synthesis or by enzymatic or chemical cleavage of the polypeptide or antibody, if applicable. Other types of covalent modifications can be introduced by reacting targeted amino acid residues with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues.

Cysteinyl residues most commonly are reacted with α-haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Cysteinyl residues also are derivatized by reaction with bromotrifluoroacetone, .alpha.-bromo-β-(5-imidozoyl)propionic acid, chloroacetyl phosphate, N-alkylmaleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. In some embodiments, para-bromophenacyl bromide also is useful; and the reaction is performed in 0.1 M sodium cacodylate at pH 6.0.

Lysinyl and amino-terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysinyl residues. Other suitable reagents for derivatizing .alpha.-amino-containing residues include imidoesters such as methyl picolinimidate, pyridoxal phosphate, pyridoxal, chloroborohydride, trinitrobenzenesulfonic acid, O-methylisourea, 2,4-pentanedione, and transaminase-catalyzed reaction with glyoxylate.

Arginyl residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginine residues requires that the reaction be performed in alkaline conditions because of the high pK_a of the guanidine functional group. Furthermore, these reagents may react with the groups of lysine as well as the arginine epsilon-amino group.

The specific modification of tyrosyl residues may be made, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidizole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively. Tyrosyl residues are iodinated using ^{125}I or ^{131}I to prepare labeled proteins for use in radioimmunoassay.

Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides (R-N.dbd.C.dbd.N-R'), where R and R' are different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginyl and glutaminyl residues by reaction with ammonium ions.

Glutaminyl and asparaginyl residues are frequently deamidated to the corresponding glutamyl and aspartyl residues, respectively. These residues are deamidated under neutral or basic conditions. The deamidated form of these residues falls within the scope of this invention.

Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the .alpha.-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification involves chemically or enzymatically coupling glycosides to the specific binding agent or antibody. These procedures are advantageous in that they do not require production of the polypeptide or antibody in a host cell that has glycosylation capabilities for N- or O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO87/05330 published 11 Sep. 1987, and in Aplin and Wriston, *CRC Crit. Rev. Biochem.*, pp. 259-306 (1981).

Removal of any carbohydrate moieties present on the polypeptide or antibody may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the specific binding agent or antibody to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the specific binding agent or antibody intact. Chemical deglycosylation is described by Hakimuddin, et al., *Arch. Biochem. Biophys.*, 259: 52 (1987) and by Edge et al., *Anal. Biochem.*, 118: 131 (1981). Enzymatic cleavage of carbohydrate moieties on a specific binding agent or antibody can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., *Meth. Enzymol.*, 138: 350 (1987).

Another type of covalent modification of an anti-hepcidin antibody described herein comprises linking the polypeptide, specific binding agent or antibody to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, polyoxyethylated polyols, polyoxy-

ethylated sorbitol, polyoxyethylated glucose, polyoxyethylated glycerol, polyoxyalkylenes, or polysaccharide polymers such as dextran. Such methods are known in the art, see, e.g. U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192, 4,179,337, 4,766,106, 4,179,337, 4,495,285, 4,609,546 or EP 315 456.

Diagnostic Methods for Hepcidin-Related Disorders and Monitoring of Therapy with Anti-Hepcidin Antibodies

In another aspect, a method is provided of detecting human hepcidin in a sample, comprising contacting a sample from a human with any of the aforementioned antibodies under conditions that allow binding of the antibody to human hepcidin, and detecting the bound antibody. In one embodiment, a first antibody to hepcidin is immobilized on a solid support, as a capture reagent, and a second antibody to hepcidin is used as a detection reagent. In a related aspect, the amount of hepcidin in the sample is quantitated by measuring the amount of the bound antibody. The detection methods can be used in a variety of diagnostic, prognostic and monitoring methods, including methods of diagnosing a hepcidin-related disorder, methods of differentiating an inflammatory disease from a non-inflammatory disease and methods of monitoring therapy with an anti-hepcidin antibody. In such methods, a level of hepcidin above a certain threshold is correlated with the presence of hepcidin-related disorder, such as hepcidin-related anemia, while a level below said threshold indicates that the patient is unlikely to have hepcidin-related disorder. Similarly, a level of hepcidin above a certain threshold is correlated with the presence of an inflammatory disease, while a level below said threshold indicates that the patient is unlikely to have an inflammatory disease. In some embodiments, such methods will diagnose patients having iron deficiency anemia, anemia of inflammation or mixed anemia. For monitoring of therapy aimed at suppressing hepcidin levels, a level of hepcidin below a certain threshold indicates that the dose of hepcidin antibody is therapeutically effective, and a level above said threshold indicates that the dose of hepcidin antibody is not therapeutically effective.

Also provided are methods for diagnosing hepcidin-related disorders, such as hepcidin-related anemia, or other diseases of hepcidin excess or hepcidin deficiency, and for monitoring the effectiveness of therapy for such a disease, including therapy with an anti-hepcidin antibody described herein. To determine the presence or absence of hepcidin-related anemia, a biological sample from a patient is contacted with one or more of the anti-hepcidin antibodies disclosed herein under conditions and for a time sufficient to allow immunocomplexes to form. Immunocomplexes formed between an anti-hepcidin antibody and hepcidin in the biological sample are then detected. The amount of hepcidin in the sample is quantitated by measuring the amount of the immunocomplex formed between the antibody and hepcidin. Within certain methods, a biological sample is isolated from a patient and is incubated with one or more of the anti-hepcidin antibodies disclosed herein, and the level of the antibody-hepcidin complex above a certain threshold is correlated with the presence of hepcidin-related anemia, and a level below said threshold indicates that the patient is unlikely to have hepcidin-related anemia. For example, a level within the normal range indicates the patient is unlikely to have hepcidin-related anemia. Normal range of serum hepcidin is generally less than 10 ng/ml when determined by certain assays, i.e., mass spectrometry techniques described in co-owned U.S. patent application Ser. No. 11/880,313 and International Publication No. WO 2008/011158, the disclosures of which are incorporated herein by reference in their entirety, but will vary depending on the assay and depending on the subset of population tested.

Also provided are methods for differentiating an inflammatory disease from a non-inflammatory disease. To determine the presence or absence of an inflammatory disease, a biological sample from a patient is contacted with one or more of the anti-hepcidin antibodies disclosed herein under conditions and for a time sufficient to allow immunocomplexes to form. Various immunoassays known in the art can be used, including but are not limited to: competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), Western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention. Antibodies: A Laboratory Manual (1988) by Harlow & Lane or more recent editions; Immunoassays: A Practical Approach, Oxford University Press, Gosling, J. P. (ed.) (2001) or more recent editions; and/or Current Protocols in Molecular Biology (Ausubel et al.), which is regularly updated. Examples of such assays usually involve the antibody attached to a surface or matrix, patient serum added and time allowed for a complex to form; suitable washing procedures to remove unbound complex, followed by either the addition of a second antibody to allow detection of the complex (a sandwich ELISA) or a detectable version of hepcidin to detect free hepcidin binding sites on the antibody surface (a competition ELISA). The level of hepcidin, as detected by the foregoing methods, above a certain threshold is correlated with the presence of an inflammatory disease, and a level below said threshold indicates that the patient is unlikely to have an inflammatory disease. A patient is unlikely to have an inflammatory disease when the hepcidin level is within the normal range. A patient is likely to have an inflammatory disease when the hepcidin level exceeds the normal range, for example 20 ng/ml, in particular, when the level is between 20 and 1000 ng/ml. Exemplary hepcidin-related inflammatory diseases include anemia of cancer, anemia of chronic disease, anemia of inflammation, chemotherapy-induced anemia, chronic kidney disease (stage I, II, III, IV or V), end stage renal disease, chronic renal failure congestive heart failure, cancer, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, *H. pyelori* infection or other bacterial infections, hepatitis C, HIV, and other viral illnesses, arteriosclerosis, atherosclerosis, cirrhosis of the liver, pancreatitis, sepsis, vasculitis, iron-deficiency, hypochromic microcytic anemia and conditions with hepcidin excess.

Within other methods, a biological sample obtained from a patient is tested for the level of hepcidin. The biological sample is incubated with one or more of the anti-hepcidin antibodies disclosed herein under conditions and for a time sufficient to allow immunocomplexes to form. Immunocomplexes formed between the hepcidin and antibodies in the biological sample that specifically bind to the hepcidin are then detected. A biological sample for use within such methods may be any sample obtained from a patient that is expected to contain hepcidin. Suitable biological samples

include blood, sera, plasma, urine and bone marrow. Suitable antibodies include antibodies from human cells, rodent, rabbit, goat, camel, or any other species.

The biological sample is incubated with antibodies in a reaction mixture under conditions and for a time sufficient to permit immunocomplexes to form between hepcidin and antibodies that are immunospecific for hepcidin. For example, a biological sample and one or more anti-hepcidin antibodies may be incubated at 4° C. for 24-48 hours.

Following the incubation, the reaction mixture is tested for the presence of immuno-complexes. Detection of immunocomplexes formed between an anti-hepcidin antibody and hepcidin present in the biological sample may be accomplished by a variety of known techniques, such as radioimmunoassays (RIA) and enzyme linked immunosorbent assays (ELISA). Suitable assays are well known in the art and are amply described in the scientific and patent literature (Harlow and Lane, 1988). Assays that may be used include, but are not limited to, the double monoclonal antibody sandwich immunoassay technique (U.S. Pat. No. 4,376,110); monoclonal-polyclonal antibody sandwich assays (Wide L., "Solid Phase Antigen-Antibody Systems," *Radioimmunoassay Methods: European Workshop Sep.* 15-17 1970 Edinburgh, Kirkham and Hunter, eds., (Churchill Livingston, Edenburgh, (1971)) pp. 405-412; the "western blot" method (U.S. Pat. No. 4,452, 901); immunoprecipitation of labeled ligand (Brown et al., *J. Biol. Chem.* 4980-4983m 1980); enzyme-linked immunosorbent assays; immunocytochemical techniques, including the use of fluorochromes (Brooks et al., *Clin. Exp. Immunol.,* 39: 477, 1980); and neutralization of activity (Bowen-Pope et al., *Science,* 226:701-703, 1984). Other immunoassays include, but are not limited to, those described in U.S. Pat. Nos. 3,850, 752; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; and 4,098,876.

For detection purposes, an anti-hepcidin antibody may either be labeled or unlabeled. Unlabeled antibodies may be used in agglutination assays or in combination with labeled detection reagents that bind to the immunocomplexes (e.g., anti-immunoglobulin, protein G, Protein A or a lectin and secondary antibodies, or antigen-binding fragments thereof, capable of binding to the antibodies that specifically bind to the hepcidin). If the anti-hepcidin antibody is labeled, the reporter group may be any suitable reporter group known in the art, including radioisotopes, fluorescent groups (e.g. fluorescein or rhodamine), luminescent groups, enzymes, biotin and dye particles. Labels that are themselves directly detectable include fluorescent or luminescent dyes, metals or metal chelates, electrochemical labels, radionuclides (e.g., 32P, 14C, 125I, 3H, or 131I), magnetic labels or beads (e.g., DYNABEADS), paramagnetic labels, or colorimetric labels (e.g., colloidal gold, colored glass or plastic beads). Such detectable labels may be directly conjugated to the anti-hepcidin antibody or detection reagent or may be associated with a bead or particle that is attached to the anti-hepcidin antibody or detection reagent. Labels that are detectable through binding of a labeled specific binding partner include biotin, digoxigenin, maltose, oligohistidine, 2,4-dinitrobenzene, phenylarsenate, ssDNA, or dsDNA). Indirect labels that can be indirectly detected by their production of a detectable reaction product include various enzymes well known in the art, such as alkaline phosphatase, horseradish peroxidase, β-galactosidase, xanthine oxidase, glucose oxidase or other saccharide oxidases, or luciferases, which cleave appropriate substrate to form a colored or fluorescent reaction product.

Within certain assays, an unlabeled anti-hepcidin antibody is immobilized on a solid support, for use as a "capture agent" (or reagent) that captures the hepcidin within a biological sample. The solid support may be any material known to those of ordinary skill in the art to which the antibody may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a tube, bead, particle or disc, such as glass, fiberglass, latex or a plastic material such as polyethylene, polypropylene, polystyrene or polyvinylchloride or a porous matrix. Other materials include agarose, dextran, polyacrylamide, nylon, Sephadex, cellulose or polysaccharides. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Pat. No. 5,359,681. The immobilized anti-hepcidin antibody may be a polyclonal antibody, or one or more monoclonal antibodies such as those described herein, or a combination of polyclonal and one or more monoclonal antibodies. The antibody may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is contemplated. In such cases, adsorption may be achieved by contacting the anti-hepcidin antibody, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (including polystyrene or polyvinylchloride) with an amount of peptide ranging from about 10 ng to about 10 μg, about 100 ng to about 1 μs, is sufficient to immobilize an adequate amount of peptide.

Following immobilization, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, including bovine serum albumin, Tween™ 20™ (Sigma Chemical Co., St. Louis, Mo.), heat-inactivated normal goat serum (NGS), or BLOTTO (buffered solution of nonfat dry milk which also contains a preservative, salts, and an antifoaming agent) can be used. The support is then incubated with a biological sample suspected of containing hepcidin. The sample can be applied neat, or, more often, it can be diluted, usually in a buffered solution which contains a small amount (0.1%-5.0% by weight) of protein, such as BSA, NGS, or BLOTTO. In general, an appropriate contact time (i.e., incubation time) is a period of time that is sufficient to detect the presence of antibody or an antigen binding fragment that is immunospecific for the hepcidin within a sample containing hepcidin. In some embodiments, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound antibody or antibody fragment. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween™ 20. A detection reagent that binds to the hepcidin in the immunocomplexes (formed by binding of the capture agent and the hepcidin from the sample) may then be added. Such detection reagent may be a polyclonal antibody, or one or more monoclonal antibodies such as those described herein, or a combination of polyclonal and one or more monoclonal antibodies such as those described herein or a Fab fraction of any antibody. The detection reagent may

be directly labeled, i.e., comprises at least a first detectable label or "reporter" molecule. Alternatively, the detection reagent may be an unlabeled anti-hepcidin antibody. This unlabeled anti-hepcidin (primary) antibody is then detected by the binding of a labeled secondary antibody or reagent to the primary antibody. For example, if the primary antibody is a murine immunoglobulin, the secondary antibody may be a labeled anti-murine immunoglobulin antibody. Similarly, if the primary antibody is a rabbit immunoglobulin, the secondary antibody may be a labeled anti-rabbit immunoglobulin antibody.

The detection reagent is incubated with the immunocomplex for an amount of time sufficient to detect the bound antibody or antigen binding fragment thereof. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound label or detection reagent is then removed and bound label or detection reagent is detected using a suitable assay or analytical instrument. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive labels, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent or chemiluminescent moieties and various chromogens, fluorescent labels and such like. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups (including horseradish peroxidase, β-galactosidase, alkaline phosphatase and glucose oxidase) may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products. Regardless of the specific method employed, a level of bound detection reagent that is at least two fold greater than background (i.e., the level observed for a biological sample obtained from an individual with a normal level of hepcidin) indicates the presence of a disorder associated with expression of hepcidin.

In alternative embodiments, the sample and detection reagent may be contacted simultaneously with the capture agent, rather than sequentially added. In yet another alternative, the sample and detection reagent may be pre-incubated together, then added to the capture agent. Other variations are readily apparent to one of ordinary skill in the art.

In another embodiment, the amount of hepcidin present in a sample is determined by a competitive binding assay. Competitive binding assays rely on the ability of a labeled standard (e.g., a hepcidin polypeptide, or an immunologically reactive portion thereof) to compete with the test sample analyte (a hepcidin polypeptide) for binding with a limited amount of an anti-hepcidin antibody. Following separation of free and bound hepcidin, the hepcidin is quantitated by relating ratio of bound/unbound hepcidin to known standards. The amount of a hepcidin polypeptide in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies typically are immobilized on a solid support so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte which remain unbound. Thus, in such embodiments, also contemplated is contacting a biological sample with labeled mature hepcidin (or a labeled fragment thereof that retains the antigenicity of hepcidin) and an antibody that binds to mature hepcidin, and detecting the amount of antibody-labeled hepcidin complex formed.

Preparation of conjugates to solid supports or detectable labels often comprise the use of chemical cross-linkers. Cross-linking reagents contain at least two reactive groups, and are divided generally into homofunctional cross-linkers (containing identical reactive groups) and heterofunctional cross-linkers (containing non-identical reactive groups). Homobifunctional cross-linkers that couple through amines, sulfhydryls or react non-specifically are available from many commercial sources. Maleimides, alkyl and aryl halides, alpha-haloacyls and pyridyl disulfides are thiol reactive groups. Maleimides, alkyl and aryl halides, and alpha-haloacyls react with sulfhydryls to form thiol ether bonds, whereas pyridyl disulfides react with sulfhydryls to produce mixed disulfides. The pyridyl disulfide product is cleavable. Imidoesters are also very useful for protein-protein cross-links.

Heterobifunctional cross-linkers possess two or more different reactive groups that allow for sequential conjugations with specific groups of proteins, minimizing undesirable polymerization or self-conjugation. Heterobifunctional reagents are also used when modification of amines is problematic. Amines may sometimes be found at the active sites of macromolecules, and the modification of these may lead to the loss of activity. Other moieties such as sulfhydryls, carboxyls, phenols and carbohydrates may be more appropriate targets. A two-step strategy allows for the coupling of a protein that can tolerate the modification of its amines to a protein with other accessible groups. A variety of heterobifunctional cross-linkers, each combining different attributes for successful conjugation, are commercially available. Cross-linkers that are amine-reactive at one end and sulfhydryl-reactive at the other end are quite common. If using heterobifunctional reagents, the most labile group is typically reacted first to ensure effective cross-linking and avoid unwanted polymerization.

As described in copending U.S. patent application Ser. No. 12/022,515, the disclosure of which is incorporated by reference herein in its entirety, it is the level of mature hepcidin (amino acids 60-84 of SEQ ID NO: 8) rather than the level of prohepcidin (amino acids 25-84 of SEQ ID NO: 8) which is diagnostic for certain disease states such as anemia of inflammation and anemia of cancer. Thus, in one preferred embodiment, antibody(ies) that bind to mature, properly folded, hepcidin (SEQ ID NO: 9) are used as both capture agent and detection reagent. Antibodies that bind to the naturally occurring N-terminally truncated versions (e.g. lacking up to two or up to five of the N-terminal amino acids of mature hepcidin) may also be used. Various combinations of capture agent and detection reagent are contemplated. For example, the capture agent may be a monoclonal antibody that binds to a first epitope of mature hepcidin and the detection reagent may be a different monoclonal antibody that binds to a second epitope of mature hepcidin. In some embodiments, antibodies specific for different epitopes of hepcidin are used, in order to minimize competition or interference between the capture agent and detection reagent. Alternatively, the capture agent may be a polyclonal antibody that binds to mature hepcidin and the detection reagent may be a monoclonal antibody. As yet another alternative, the capture agent may be a monoclonal antibody that binds to mature hepcidin and the detection reagent may be a polyclonal antibody. In any of the preceding embodiments, either the capture agent or the detection reagent may be a combination of a polyclonal and a monoclonal antibody.

In some embodiments, a mature-hepcidin-specific monoclonal antibody is used as either the capture agent or detection reagent or both. A mature-hepcidin-specific antibody does not bind prohepcidin at all, or binds to prohepcidin with such low affinity that the antibody can differentiate mature hepcidin from prohepcidin. For example, such a monoclonal antibody may bind to the N-terminus of mature hepcidin, or it

may bind an epitope of mature hepcidin that is not detectable in prohepcidin (e.g. due to masking by the prodomain).

In embodiments utilizing a monoclonal antibody that binds to an epitope present in both mature hepcidin and prohepcidin, an optional further refinement is contemplated. The amount of mature hepcidin alone is determined by subtracting the amount of prohepcidin present in the sample from the amount of total hepcidin (prohepcidin plus mature hepcidin) present in the same sample. The amount of prohepcidin can be determined by using prohepcidin-specific polyclonal and/or monoclonal antibodies in techniques like those described above. A prohepcidin-specific antibody does not bind mature hepcidin at all, or binds to mature hepcidin with such low affinity that the antibody can differentiate prohepcidin from mature hepcidin. For example, such antibodies may bind to a linear or conformational epitope present uniquely in the prodomain of hepcidin (amino acids 25-59 of SEQ ID NO: 8). In such embodiments, the amount of total hepcidin and prohepcidin may be determined sequentially or simultaneously. Because prohepcidin is rapidly degraded in serum to hepcidin, in some embodiments furin inhibitors are added to the biological sample in order to prevent or reduce degradation of prohepcidin.

In some embodiments utilizing a monoclonal antibody that binds to the 25-amino acid mature hepcidin, the monoclonal antibody does not bind the degradation products (i.e., hepcidin-22 and hepcidin-20).

In one embodiment of a simultaneous assay for detecting total hepcidin and prohepcidin, the capture agent is an antibody that binds to an epitope present in both mature hepcidin and prohepcidin, and two detection reagents are applied simultaneously. The first detection reagent is a labeled antibody that binds to an epitope present in both mature hepcidin and prohepcidin and the second detection reagent is a differently labeled prohepcidin-specific antibody. For example, the first detection reagent is labeled with a fluorescent dye detectable at a first wavelength while the second detection reagent is labeled with a fluorescent dye detectable at a second wavelength. Thus, in such an example, the capture agent will bind total hepcidin (mature hepcidin plus prohepcidin) in the sample, the first detection reagent will detect the amount of total hepcidin, and the second detection reagent will detect the amount of prohepcidin. Subtracting the amount of prohepcidin from amount of the total hepcidin will yield the amount of mature hepcidin. In other alternative embodiments, two different capture agents may be used: a first capture agent that binds to an epitope present in both mature hepcidin and prohepcidin, and a second capture agent that is a prohepcidin-specific antibody, optionally with a detection reagent that binds an epitope present in both mature hepcidin and prohepcidin.

Other embodiments for carrying out simultaneous assays are well known in the art, including the multiplex system described, e.g., in Khan et al., *Clin. Vaccine Immunol.,* 13(1) 45-52 (January 2006) involving differentially coded sets of fluorescent microbeads. Other embodiments for performing multiple simultaneous assays on a single surface include surfaces having a plurality of discrete, addressable locations for the detection of a plurality of different analytes. Such formats include protein microarrays, or "protein chips" (see, e.g., Ng and Ilag, J. Cell Mol. Med. 6: 329-340 (2002)) and capillary devices (see, e.g., U.S. Pat. No. 6,019,944). In these embodiments, each discrete surface location has a different antibody that immobilizes a different analyte for detection at each location. Surfaces can alternatively have one or more discrete particles (e.g., microparticles or nanoparticles) immobilized at discrete locations of a surface, of which each set of particles contains a different capture agent for a different analyte.

Complementary antibody pairs (antibodies that bind to different epitopes on hepcidin such that the pairs are suitable for use in sandwich assays) were difficult to identify. Use of complementary pairs that minimize competition or interference can increase sensitivity of the assay by 20-fold to 50-fold. In some embodiments, the immunoassays described herein are capable of measuring hepcidin levels ranging from 0.01 ng/mL to 10 μg/mL.

Antibody pairs suitable for use in sandwich immunoassays include the following: (1) when one antibody of the pair is an antibody binds to the same epitope as antibody is 1S1, or competes with antibody 1S1 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, a suitable second antibody may be: (a) an antibody that binds to the same epitope as antibody is 23F11, or competes with antibody 23F11 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more; or (b) an antibody that binds to the same epitope as antibody is 15E1, or competes with antibody 15E1 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more; or (c) an antibody that binds to the same epitope as antibody is 12B9, or competes with antibody 12B9 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more; (2) when one antibody of the pair is an antibody that binds to the same epitope as antibody 12B9 or competes with antibody 12B9 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, a suitable second antibody may be: (a) an antibody that binds to the same epitope as antibody 18D8, or competes with antibody 18D8 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, or (b) an antibody that binds to the same epitope as antibody 19C1, or competes with antibody 19C1 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, or (c) an antibody that binds to the same epitope as antibody 19D12, or competes with antibody 19D12 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, or (d) an antibody that binds to the same epitope as antibody 19H6, or competes with antibody 19H6 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more; or (e) an antibody that binds to the same epitope as antibody 1S1 or competes with antibody 1S1 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more; or (3) when one antibody o the pair is an antibody that binds to the same epitope as antibody 23F11, or competes with antibody 23F11 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, a suitable second antibody may be: (a) an antibody that binds to the same epitope as antibody 18D8, or competes with antibody 18D8 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, or (b) an antibody that binds to the same epitope as antibody 19C1, or competes with antibody 19C1 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, or (c) an antibody that binds to the same epitope as antibody 19D12, or competes with antibody 19D12 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, or (d) an antibody that binds to the same epitope as antibody 19H6, or competes with antibody 19H6 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more; or (e) an antibody that binds to the same epitope as antibody 1S1

or competes with antibody 4E1 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more; or (f) an antibody that binds to the same epitope as antibody 3B3 or competes with antibody 3B3 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more; (4) when one antibody of the pair is an antibody binds to the same epitope as antibody 15E1, or competes with antibody 15E1 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more, a suitable second antibody may be: (a) an antibody that binds to the same epitope as antibody 1S1, or competes with antibody 1S1 for binding to mature human hepcidin of SEQ ID NO: 9 by at least about 75%, 80%, 85%, 90% or more.

In some embodiments, methods for monitoring the effectiveness of therapy with an anti-hepcidin antibody include monitoring changes in the level of hepcidin in a sample, or in an animal such as a human patient. Methods in which hepcidin levels are monitored may comprise (a) incubating a first biological sample, obtained from a patient prior to a therapy with one or more of the anti-hepcidin antibodies disclosed herein, wherein the incubation is performed under conditions and for a time sufficient to allow immunocomplexes to form; (b) detecting immunocomplexes formed between the hepcidin in the biological sample and antibodies or antigen binding fragments that specifically bind hepcidin; and optionally (c) repeating steps (a) and (b) using a second biological sample taken from the patient at later time, such as for example, following therapy with one or more of the anti-hepcidin antibodies disclosed herein; and (d) comparing the number of immunocomplexes detected in the first and second biological samples.

Other monitoring methods include measuring (a) the blood (e.g., serum or plasma) circulating level of complexes between hepcidin and the therapeutic agent, and optionally (b) the amount of free hepcidin present in circulation. For example, complexes between hepcidin and therapeutic antibody can be detected using an anti-human Fc antibody that binds to the therapeutic antibody part of the complex and an Fab fragment of a "pairing" anti-hepcidin antibody that binds to the hepcidin part of the complex. Alternatively, an anti-idiotypic antibody can be used in place of the anti-human Fc antibody. As another alternative, an anti-hepcidin antibody containing a non-human Fc (e.g. a human Fc is replaced with murine Fc) can be used in place of the Fab fragment.

As another example, free hepcidin can be detected after removing hepcidin-therapeutic antibody complexes from the biological sample, using either an anti-human Fc antibody or an anti-idiotypic antibody that has been immobilized on a solid support. The amount of free hepcidin which remains unbound to the solid support is then measured. This level of free hepcidin may reflect the effectiveness of the therapeutic antibody in removing available circulating hepcidin.

A biological sample for use within such methods may be any sample obtained from a patient that would be expected to contain hepcidin. Exemplary biological samples include blood, plasma, sera, urine and bone marrow. A first biological sample may be obtained prior to initiation of therapy or part way through a therapy regime. The second biological sample should be obtained in a similar manner, but at a time following additional therapy. The second biological sample may be obtained at the completion of, or part way through, therapy, provided that at least a portion of therapy takes place between the isolation of the first and second biological samples.

Incubation and detection procedures for both samples may generally be performed as described above. A decrease in the number of immunocomplexes in the second sample relative to the first sample indicates a decrease in hepcidin levels and reflects successful therapy. Free serum hepcidin may also be analyzed in a similar manner, and a decrease in free serum hepcidin indicates successful therapy.

Hepcidin-related disorders, inflammatory diseases, and diseases or disorders of iron homeostasis for which the diagnostic or monitoring methods may be useful include but are not limited to african iron overload, alpha thalassemia, Alzheimer's disease, anemia, anemia of cancer, anemia of chronic disease, anemia of inflammation, arteriosclerosis or atherosclerosis (including coronary artery disease, cerebrovascular disease or peripheral occlusive arterial disease), ataxias, ataxias related to iron, atransferrinemia, cancer, ceruloplasmin deficiency, chemotherapy-induced anemia, chronic renal/kidney disease (stage I, II, III, IV or V), including end stage renal disease or chronic renal/kidney failure, cirrhosis of liver, classic hemochromatosis, collagen-induced arthritis (CIA), conditions with hepcidin excess (elevated hepcidin), congenital dyserythropoietic anemia, congestive heart failure, Crohn's disease, diabetes, disorders of iron biodistribution, disorders of iron homeostasis, disorders of iron metabolism, ferroportin disease, ferroportin mutation hemochromatosis, folate deficiency, Friedrich's ataxia, funicular myelosis, gracile syndrome, *H. pyelori* infection or other bacterial infections, Hallervordan Spatz disease, hemochromatosis, hemochromatosis resulting from mutations in transferrin receptor 2, hemoglobinopathies, hepatitis, hepatitis (Brock), hepatitis C, hepatocellular carcinoma, hepcidin deficiency, hereditary hemochromatosis, HIV or other viral illnesses, Huntington's disease, hyperferritinemia, hypochromic microcytic anemia, hypoferremia, insulin resistance, iron deficiency anemia, iron deficiency disorders, iron overload disorders, iron-deficiency conditions with hepcidin excess, juvenile hemochromatosis (HFE2), multiple sclerosis, mutation in transferrin receptor 2, FIFE, hemojuvelin, ferroportin or other genes of iron metabolism, neonatal hemochromatosis, neurodegenerative diseases related to iron, osteopenia, osteoporosis pancreatitis, Pantothenate kinase-associated neurodegeneration, Parkinson's disease, pellagra, pica, porphyria, porphyria cutanea tarda, pseudoencephalitis, pulmonary hemosiderosis, red blood cell disorders, rheumatoid arthritis, sepsis, sideroblastic anemia, systemic lupus erythematosus, thalassemia, thalassemia intermedia, transfusional iron overload, tumors, vasculitis, vitamin B6 deficiency, vitamin B12 deficiency, and/or Wilson's disease.

Methods of setting an appropriate threshold for diagnosis of the disease states described herein and prognostic monitoring as described herein are well known in the art. By way of example, levels of hepcidin in a fluid sample from a sufficient representative number of normal subjects (e.g. healthy population without the condition to be detected) are analyzed relative to the hepcidin level from a sufficient representative number of diseased subjects (e.g. population confirmed to have the disease or condition) using the same protocols. A threshold cutoff can be determined that differentiates most of the normal population from most of the diseased population. Alternatively, useful end point values for negative, uncertain and positive results can be determined from the data. For example, a normal range (indicative of a negative result) can be determined, which includes hepcidin of most of the normal population but which exclude almost all of the diseased population. Correspondingly, a range indicative of a positive result can be determined, which includes hepcidin of most of the diseased population but which exclude almost all of the normal population. Similarly, a threshold differentiating hepcidin levels in a population suffering from anemia of inflammation from hepcidin levels in a population suffering from

iron deficiency anemia can be determined. Useful endpoint values may indicate that the patient is suffering from anemia of inflammation, iron deficiency anemia or mixed anemia. Appropriate endpoint values for the threshold may be determined to optimize the desired specificity or sensitivity, and may also take account of overall medical and epidemiological factors. Factors to be considered include the clinical objective of the laboratory test and whether it is necessary to have a high positive predictive value, or a high negative predictive value, as well as prevalence of the disease in the test population.

Therapeutic Uses for Anti-Hepcidin Antibodies

Also provided is the use of anti-hepcidin antibodies described herein that specifically bind human hepcidin, to treat subjects in need thereof. In some embodiments, the subject may be at risk of or suffering from an elevated level of hepcidin, a hepcidin-related disorder, a disorder of iron homeostasis, or anemia.

As used herein, "treatment" or "treat" refers to both prophylactic treatment of a subject at risk of, or having a predisposition toward, a disease or disorder, and to therapeutic treatment of a subject suffering from a disease or disorder.

Administration of a therapeutic agent in a prophylactic method can occur prior to the manifestation of symptoms of an undesired disease or disorder, such that the disease or disorder is prevented or, alternatively, delayed in its progression. Thus, when used in conjunction with prophylactic methods, the term "therapeutically effective" means that, after treatment, a fewer number of subjects (on average) develop the undesired disease or disorder or progress in severity of symptoms.

When used in conjunction with therapeutic methods involving administration of a therapeutic agent after the subject manifests symptoms of a disease or disorder, the term "therapeutically effective" means that, after treatment, one or more signs or symptoms of the disease or disorder is ameliorated or eliminated.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. In some embodiments, the mammal is human.

As used herein, a "hepcidin-related disorder" refers to a condition caused by or associated with an abnormal level of hepcidin (e.g., hepcidin excess or hepcidin deficiency relative to the degree of anemia or iron stored) which disrupts iron homeostasis. A disruption in iron homeostasis can in turn result in secondary diseases such as anemia. Acute or chronic inflammatory conditions can result in upregulation of hepcidin expression, which can result in decreased circulating iron levels, which can cause anemia or worsen existing anemia. Exemplary hepcidin-related inflammatory diseases include anemia of cancer, anemia of chronic disease, anemia of inflammation, chemotherapy-induced anemia, chronic kidney disease (stage I, II, III, IV or V), end stage renal disease, chronic renal failure congestive heart failure, cancer, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, *H. pyelori* infection or other bacterial infections, hepatitis C, HIV, and other viral illnesses, arteriosclerosis, atherosclerosis, cirrhosis of the liver, pancreatitis, sepsis, vasculitis, iron-deficiency, hypochromic microcytic anemia and conditions with hepcidin excess.

As used herein, the phrase "disease (or disorder) of iron homeostasis" refers to a condition in which a subject's iron levels require modulation. It includes hepcidin-related disorders; conditions not associated with elevated levels of hepcidin that nevertheless would benefit from inhibition of hepcidin activity, such as a disruption in iron homeostasis not caused by hepcidin; diseases where aberrant iron absorption, recycling, metabolism or excretion causes a disruption in normal iron blood levels or tissue distribution; diseases where iron dysregulation is a consequence of another disease or condition, such as inflammation, cancer or chemotherapy; diseases or disorders resulting from abnormal iron blood levels or tissue distribution; and diseases or disorders that can be treated by modulating iron levels or distribution. Nonlimiting examples of such diseases or disorders of iron homeostasis, hepcidin-related disorders and inflammatory conditions which can result in hepcidin excess include african iron overload, alpha thalassemia, Alzheimer's disease, anemia, anemia of cancer, anemia of chronic disease, anemia of inflammation, arteriosclerosis or atherosclerosis (including coronary artery disease, cerebrovascular disease or peripheral occlusive arterial disease), ataxias, ataxias related to iron, atransferrinemia, cancer, ceruloplasmin deficiency, chemotherapy-induced anemia, chronic renal/kidney disease (stage I, II, III, IV or V), including end stage renal disease or chronic renal/kidney failure, cirrhosis of liver, classic hemochromatosis, collagen-induced arthritis (CIA), conditions with hepcidin excess (elevated hepcidin), congenital dyserythropoietic anemia, congestive heart failure, Crohn's disease, diabetes, disorders of iron biodistribution, disorders of iron homeostasis, disorders of iron metabolism, ferroportin disease, ferroportin mutation hemochromatosis, folate deficiency, Friedrich's ataxia, funicular myelosis, gracile syndrome, *H. pyelori* infection or other bacterial infections, Hallervordan Spatz disease, hemochromatosis, hemochromatosis resulting from mutations in transferrin receptor 2, hemoglobinopathies, hepatitis, hepatitis (Brock), hepatitis C, hepatocellular carcinoma, hereditary hemochromatosis, HIV or other viral illnesses, Huntington's disease, hyperferritinemia, hypochromic microcytic anemia, hypoferremia, insulin resistance, iron deficiency anemia, iron deficiency disorders, iron overload disorders, iron-deficiency conditions with hepcidin excess, juvenile hemochromatosis (HFE2), multiple sclerosis, mutation in transferrin receptor 2, HFE, hemojuvelin, ferroportin or other genes of iron metabolism, neonatal hemochromatosis, neurodegenerative diseases related to iron, osteopenia, osteoporosis pancreatitis, Pantothenate kinase-associated neurodegeneration, Parkinson's disease, pellagra, pica, porphyria, porphyria cutanea tarda, pseudoencephalitis, pulmonary hemosiderosis, red blood cell disorders, rheumatoid arthritis, sepsis, sideroblastic anemia, systemic lupus erythematosus, thalassemia, thalassemia intermedia, transfusional iron overload, tumors, vasculitis, vitamin B6 deficiency, vitamin B12 deficiency, and/or Wilson's disease.

Non-inflammatory conditions which are implicated in a disruption of iron regulation include, but are not limited to, vitamin B6 deficiency, vitamin B12 deficiency, folate deficiency, pellagra, funicular myelosis, pseudoencephalitis, Parkinson's disease (Fasano et al., *J. Neurochem.* 96:909 (2006) and Kaur et al., *Ageing Res. Rev.,* 3:327 (2004)), Alzheimer's disease, coronary heart disease, osteopenia and osteoporosis (Guggenbuhl et al., *Osteoporos. Int.* 16:1809 (2005)), hemoglobinopathies and other disorders of red cell metabolism (Papanikolaou et al., *Blood* 105:4103 (2005)), and peripheral occlusive arterial disease.

Various other iron indices and their normal ranges of concentrations are listed in Table 2.

TABLE 2

Iron Index	Normal Level (Range)
Serum iron	50-170 μg/dL
Hemoglobin	11.5-18 g/dL
Hematocrit	37-54%
Red blood cell count (RBC)	4.6-6.2 × 10^{12} cells/L (men) 4.25-5.4 × 10^{12} cells/L (women)
Mean Corpuscular Hemoglobin (MCH)	27-32 pg
Mean Corpuscular Hemoglobin Concentration (MCHC)	32-36%
Mean Corpuscular Volume (MCV)	80-96 fL
Red Cell Distribution Width (RDW)	11.5-14.5% (electrical impedence method) or 10.2-11.8% (laser light method)
Reticulocyte count	18-158 × 10^{9} cells/L (0.8-2.5% in men; 0.8-4% in women)
Total Iron Binding Capacity (TIBC)	250-450 μg/dL
Transferrin Iron Saturation Percentage (Tsat)	15-50%
Ferritin	12-120 μg/L
Folate	3-16 ng/mL (serum) and 130-628 ng/mL (red blood cell)
Vitamin B12	200-900 pg/ml

A patient's iron index level outside of the normal ranges listed in Table 2 indicates that the patient may benefit from treatment with an anti-hepcidin antibody described herein. Since hepcidin plays a key role in iron homeostasis, hepcidin levels and activity will correlate to a disruption of iron homeostasis and/or iron indices. Elevated hepcidin levels correlate with serum iron levels below the normal ranges indicated in Table 2, low hemoglobin, and hematocrit, reduced or normal Tsat and high or normal ferritin values, and elevated inflammatory status as measured by C-reactive protein (CRP) elevation or other markers of inflammation.

As used herein, the phrase "therapeutically effective amount" of an anti-hepcidin antibody described herein refers to an amount that results in the desired therapeutic effect (i.e. that provides "therapeutic efficacy"). Exemplary therapeutic effects include increased circulating iron levels or increased iron availability, increased red blood cell count, increased red blood cell mean cell volume, increased red blood cell hemoglobin content, increased hemoglobin (e.g., increased by ≥0.5 g/dL), increased hematocrit, increased Tsat, increased reticulocyte count, increased or normalized reticulocyte mean cell volume, increased reticulocyte hemoglobin content, or reduced free hepcidin levels in serum or plasma, or normalization of any of the parameters described above. Returning such a parameter to its normal range is not required for therapeutic efficacy; for example, a measurable change (increase or reduction) in the direction of normal can be considered to be a desired therapeutic effect by a clinician. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. For example, in aspects where the anti-hepcidin antibody is administered in conjunction with an enrythropoiesis stimulator, a therapeutically effective amount is meant to refer to the combined amount that increases or normalizes any of the parameters stated above.

In order to facilitate the diagnosis of patients, decision trees, such as that of FIG. **14**B, can be used to interpret the level of the hepcidin, and which is used to assist the user or interpreter in determining a course of treatment and the significance of the concentration reading. Hepcidin values are predicted to be elevated in patients with inflammation iron overload and ferroportin disease and suppressed in patients with hemochromatosis, hemoglobinopathies, and other red cell disorders. The decision tree of FIG. **14**B shows how measurement of hepcidin levels simplifies diagnosis and/or assessment of a patient suspected of having iron metabolism disorders. FIG. **14**A shows the decision tree assessment without a measurement of hepcidin levels.

The compositions for and methods of treatment described herein may utilize one or more anti-hepcidin antibodies described herein used singularly or in combination with other therapeutic agents to achieve the desired effects.

Combination Therapy

It may be further advantageous to mix two or more antibodies together (which bind to the same or different target antigens) or to co-administer an antibody described herein with a second therapeutic agent to provide still improved efficacy. Concurrent administration of two therapeutic agents does not require that the agents be administered at the same time or by the same route, as long as there is an overlap in the time period during which the agents are exerting their therapeutic effect. Simultaneous or sequential administration is contemplated, as is administration on different days or weeks.

In some embodiments, the methods described herein include the administration of single antibodies, as well as combinations, or "cocktails", of different antibodies. Such antibody cocktails may have certain advantages inasmuch as they contain antibodies which exploit different effector mechanisms. Such antibodies in combination may exhibit synergistic therapeutic effects.

Combination therapy using an anti-hepcidin antibody described herein and an erythropoiesis stimulator is specifically contemplated. In various embodiments, anti-hepcidin antibodies and erythropoiesis stimulators can be used to improve treatment of a patient with anemia. In particular, patients who are hypo-responsive to, including unresponsive or resistant to, erythropoiesis stimulator therapy, such as erythropoietin or analogs thereof (Epoetin alfa, Epoetin beta, darbepoetin alfa), among others, will benefit from co-treatment with an anti-hepcidin antibody described herein. In one embodiment, combination therapy includes treatment with at least one antibody that binds to human hepcidin and at least one erythropoiesis stimulator.

Combination therapy using an anti-hepcidin antibody and an iron chelator to redistribute iron stores in the body is also contemplated. An iron chelator is an agent capable of binding iron and removing it from a tissue or from circulation. Examples include deferoxamine (Desferal®) and deferasirox (Exjade®), and deferiprone (1,2-dimethyl-3-hydroxypyridin-4-one). In some embodiments, anti-hepcidin antibodies and erythropoiesis stimulators can be used to improve treatment of a patient an iron loading disorder secondary to transfusion-dependent iron overload, or have an iron maldistribution disorder such as Friedreich's ataxia.

As used herein, "erythropoiesis stimulator" means a chemical compound that directly or indirectly causes activation of the erythropoietin receptor, for example, by binding to and causing dimerization of the receptor or by stimulating endogenous erythropoietin expression. Erythropoiesis stimulators include erythropoietin and variants, analogs, or derivatives thereof that bind to and activate erythropoietin receptor; antibodies that bind to erythropoietin receptor and activate the receptor; or peptides that bind to and activate erythropoietin receptor; or small organic chemical compounds, option-

ally less than about 1000 Daltons in molecular weight, that bind to and activate erythropoietin receptor. Erythropoiesis stimulators include, but are not limited to, epoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin iota, epoetin zeta, and analogs thereof, pegylated erythropoietin, carbamylated erythropoietin, mimetic peptides (including EMP1/hematide), mimetic antibodies and HIF inhibitors (see U.S. Patent Application Publication No. 2005/0020487, the disclosure of which is incorporated by reference in its entirety). Exemplary erythropoiesis stimulators include erythropoietin, darbepoetin, erythropoietin agonist variants, and peptides or antibodies that bind and activate erythropoietin receptor (and include compounds reported in U.S. Patent Application Publication Nos. 2003/0215444 and 2006/0040858, the disclosures of each of which is incorporated herein by reference in its entirety) as well as erythropoietin molecules or variants or analogs thereof as disclosed in the following patents or patent applications, which are each herein incorporated by reference in its entirety: U.S. Pat. Nos. 4,703,008; 5,441,868; 5,547,933; 5,618,698; 5,621,080; 5,756,349; 5,767,078; 5,773,569; 5,955,422; 5,830,851; 5,856,298; 5,986,047; 6,310,078; 6,391,633; 6,583,272; 6,586,398; 6,900,292; 6,750,369; 7,030,226; 7,084,245; 7,217,689; PCT publication nos. WO 91/05867; WO 95/05465; WO 99/66054; WO 00/24893; WO 01/81405; WO 00/61637; WO 01/36489; WO 02/014356; WO 02/19963; WO 02/20034; WO 02/49673; WO 02/085940; WO 03/029291; WO 2003/055526; WO 2003/084477; WO 2003/094858; WO 2004/002417; WO 2004/002424; WO 2004/009627; WO 2004/024761; WO 2004/033651; WO 2004/035603; WO 2004/043382; WO 2004/101600; WO 2004/101606; WO 2004/101611; WO 2004/106373; WO 2004/018667; WO 2005/001025; WO 2005/001136; WO 2005/021579; WO 2005/025606; WO 2005/032460; WO 2005/051327; WO 2005/063808; WO 2005/063809; WO 2005/070451; WO 2005/081687; WO 2005/084711; WO 2005/103076; WO 2005/100403; WO 2005/092369; WO 2006/50959; WO 2006/02646; WO 2006/29094; and U.S. Patent Application Publication Nos.: US 2002/0155998; US 2003/0077753; US 2003/0082749; US 2003/0143202; US 2004/0009902; US 2004/0071694; US 2004/0091961; US 2004/0143857; US 2004/0157293; US 2004/0175379; US 2004/0175824; US 2004/0229318; US 2004/0248815; US 2004/0266690; US 2005/0019914; US 2005/0026834; US 2005/0096461; US 2005/0107297; US 2005/0107591; US 2005/0124045; US 2005/0124564; US 2005/0137329; US 2005/0142642; US 2005/0143292; US 2005/0153879; US 2005/0158822; US 2005/0158832; US 2005/0170457; US 2005/0181359; US 2005/0181482; US 2005/0192211; US 2005/0202538; US 2005/0227289; US 2005/0244409; US 2006/0088906; US 2006/0111279.

Erythropoietin includes, but is not limited to, a polypeptide comprising the amino acid sequence as set forth in SEQ ID NO: 72. Amino acids i through 165 of SEQ ID NO: 72 constitute the mature protein of any molecules designated as an epoetin, e.g., epoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin iota, epoetin gamma, epoetin zeta, and the like. Additionally, an epoetin also includes any of the aforementioned epoetin which are chemically modified, e.g., with one or more water-soluble polymers such as, e.g., polyethylene glycol (including PEG-EPO-beta). Also contemplated are analogs of erythropoietin, with 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 72 still retaining erythropoietic activity.

Exemplary sequences, manufacture, purification and use of recombinant human erythropoietin are described in a number of patent publications, including but not limited to Lin U.S. Pat. No. 4,703,008 and Lai et al. U.S. Pat. No. 4,667,016, each of which is incorporated herein by reference in its entirety. Darbepoetin is a hyperglycosylated erythropoietin analog having five changes in the amino acid sequence of rHuEPO which provide for two additional carbohydrate chains. More specifically, darbepoetin alfa contains two additional N-linked carbohydrate chains at amino acid residues 30 and 88 of SEQ ID NO: 73. Exemplary sequences, manufacture, purification and use of darbepoetin and other erythropoietin analogs are described in a number of patent publications, including Strickland et al., WO 91/05867, Elliott et al., WO 95/05465, Egrie et al., WO 00/24893, and Egrie et al. WO 01/81405, each of which is incorporated herein by reference in its entirety. Derivatives of naturally occurring or analog polypeptides include those which have been chemically modified, for example, to attach water soluble polymers (e.g., pegylated), radionuclides, or other diagnostic or targeting or therapeutic moieties.

The term "erythropoietic activity" means activity to stimulate erythropoiesis as demonstrated in an in vivo assay, for example, the exhypoxic polycythemic mouse assay. See, e.g., Cotes and Bangham, *Nature* 191:1065 (1961).

Administration and Preparation of Pharmaceutical Formulations

In another aspect, pharmaceutical compositions are provided comprising a therapeutically effective amount of any of the antibodies described herein and a pharmaceutically acceptable sterile carrier, diluent or excipient. Also provided is the use of such antibodies in preparation of a medicament for treatment of a human with an elevated level of hepcidin, a hepcidin-related disorder, a disorder of iron homeostasis or an anemia. It is understood that co-administration methods involving administration of antibodies with a second therapeutic agent, as described herein, encompass not only the use of the antibody in preparation of a medicament for co-administration with the second therapeutic agent, but also the use of the second therapeutic agent in preparation of a medicament for co-administration with the antibody.

In some embodiments, the anti-hepcidin antibodies or specific binding agents used in the practice of a method described herein may be formulated into pharmaceutical compositions comprising a carrier suitable for the desired delivery method. Suitable carriers include any material which, when combined with an anti-hepcidin antibody or specific binding agent, retains the high-affinity binding of hepcidin and is nonreactive with the subject's immune systems. Examples include, but are not limited to, any of a number of standard pharmaceutical carriers such as sterile phosphate buffered saline solutions, bacteriostatic water, and the like. A variety of aqueous carriers may be used, e.g., water, buffered water, 0.4% saline, 0.3% glycine and the like, and may include other proteins for enhanced stability, such as albumin, lipoprotein, globulin, etc., subjected to mild chemical modifications or the like.

Exemplary antibody concentrations in the formulation may range from about 0.1 mg/ml to about 180 mg/ml or from about 0.1 mg/mL to about 50 mg/mL, or from about 0.5 mg/mL to about 25 mg/mL, or alternatively from about 2 mg/mL to about 10 mg/mL. An aqueous formulation of the antibody may be prepared in a pH-buffered solution, for example, at pH ranging from about 4.5 to about 6.5, or from about 4.8 to about 5.5, or alternatively about 5.0. Examples of buffers that are suitable for a pH within this range include acetate (e.g. sodium acetate), succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers. The buffer concentration can be from about 1 mM to

about 200 mM, or from about 10 mM to about 60 mM, depending, for example, on the buffer and the desired isotonicity of the formulation.

A tonicity agent, which may also stabilize the antibody, may be included in the formulation. Exemplary tonicity agents include polyols, such as mannitol, sucrose or trehalose. In some embodiments, the aqueous formulation is isotonic, although hypertonic or hypotonic solutions may be suitable. Exemplary concentrations of the polyol in the formulation may range from about 1% to about 15% w/v.

A surfactant may also be added to the antibody formulation to reduce aggregation of the formulated antibody and/or minimize the formation of particulates in the formulation and/or reduce adsorption. Exemplary surfactants include nonionic surfactants such as polysorbates (e.g. polysorbate 20, or polysorbate 80) or poloxamers (e.g. poloxamer 188). Exemplary concentrations of surfactant may range from about 0.001% to about 0.5%, or from about 0.005% to about 0.2%, or alternatively from about 0.004% to about 0.01% w/v.

In one embodiment, the formulation contains the above-identified agents (i.e. antibody, buffer, polyol and surfactant) and is essentially free of one or more preservatives, such as benzyl alcohol, phenol, m-cresol, chlorobutanol and benzethonium C1. In another embodiment, a preservative may be included in the formulation, e.g., at concentrations ranging from about 0.1% to about 2%, or alternatively from about 0.5% to about 1%. One or more other pharmaceutically acceptable carriers, excipients or stabilizers such as those described in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980) may be included in the formulation provided that they do not adversely affect the desired characteristics of the formulation. Acceptable carriers, excipients or stabilizers are nontoxic to recipients at the dosages and concentrations employed and include; additional buffering agents; co-solvents; antoxidants including ascorbic acid and methionine; chelating agents such as EDTA; metal complexes (e.g. Zn-protein complexes); biodegradable polymers such as polyesters; and/or salt-forming counterions such as sodium.

Therapeutic formulations of the anti-hepcidin antibody are prepared for storage by mixing the antibody having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, maltose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

In one embodiment, a suitable formulation contains an isotonic buffer such as a phosphate, acetate, or TRIS buffer in combination with a tonicity agent such as a polyol, Sorbitol, sucrose or sodium chloride which tonicifies and stabilizes. One example of such a tonicity agent is 5% Sorbitol or sucrose. In addition, the formulation could optionally include a surfactant such as to prevent aggregation and for stabilization at 0.01 to 0.02% wt/vol. The pH of the formulation may range from 4.5-6.5 or 4.5-5.5. Other exemplary descriptions of pharmaceutical formulations for antibodies may be found in US 2003/0113316 and U.S. Pat. No. 6,171,586, each incorporated herein by reference in its entirety.

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, those with complementary activities that do not adversely affect each other. For example, it may be desirable to further provide an immunosuppressive agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

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

Suspensions and crystal forms of antibodies are also contemplated. Methods to make suspensions and crystal forms are known to one of skill in the art.

The formulations to be used for in vivo administration must be sterile. In some embodiments, the compositions described herein may be sterilized by conventional, well known sterilization techniques. For example, sterilization is readily accomplished by filtration through sterile filtration membranes. The resulting solutions may be packaged for use or filtered under aseptic conditions and lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration.

The process of freeze-drying is often employed to stabilize polypeptides for long-term storage, particularly when the polypeptide is relatively unstable in liquid compositions. A lyophilization cycle is usually composed of three steps: freezing, primary drying, and secondary drying; Williams and Polli, *Journal of Parenteral Science and Technology*, Volume 38, Number 2, pages 48-59 (1984). In the freezing step, the solution is cooled until it is adequately frozen. Bulk water in the solution forms ice at this stage. The ice sublimes in the primary drying stage, which is conducted by reducing chamber pressure below the vapor pressure of the ice, using a vacuum. Finally, sorbed or bound water is removed at the secondary drying stage under reduced chamber pressure and an elevated shelf temperature. The process produces a material known as a lyophilized cake. Thereafter the cake can be reconstituted prior to use.

The standard reconstitution practice for lyophilized material is to add back a volume of pure water (typically equivalent to the volume removed during lyophilization), although dilute solutions of antibacterial agents are sometimes used in the production of pharmaceuticals for parenteral administration; Chen, *Drug Development and Industrial Pharmacy*, Volume 18, Numbers 11 and 12, pages 1311-1354 (1992).

Excipients have been noted in some cases to act as stabilizers for freeze-dried products; Carpenter et al., *Developments in Biological Standardization*, Volume 74, pages 225-239 (1991). For example, known excipients include polyols

(including mannitol, sorbitol and glycerol); sugars (including glucose and sucrose); and amino acids (including alanine, glycine and glutamic acid).

In addition, polyols and sugars are also often used to protect polypeptides from freezing and drying-induced damage and to enhance the stability during storage in the dried state. In general, sugars, in particular disaccharides, are effective in both the freeze-drying process and during storage. Other classes of molecules, including mono- and disaccharides and polymers such as PVP, have also been reported as stabilizers of lyophilized products.

For injection, the pharmaceutical formulation and/or medicament may be a powder suitable for reconstitution with an appropriate solution as described above. Examples of these include, but are not limited to, freeze dried, rotary dried or spray dried powders, amorphous powders, granules, precipitates, or particulates. For injection, the formulations may optionally contain stabilizers, pH modifiers, surfactants, bioavailability modifiers and combinations of these.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and y ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the Lupron Depot™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(−)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37° C., resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S—S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

In some embodiments, the formulations described herein may be designed to be short-acting, fast-releasing, long-acting, or sustained-releasing as described herein. Thus, the pharmaceutical formulations may also be formulated for controlled release or for slow release.

Therapeutically effective amounts of a composition will vary and depend on the severity of the disease and the weight and general state of the subject being treated, but generally range from about 1.0 μg/kg to about 100 mg/kg body weight, or about 10 μg/kg to about 30 mg/kg, or about 0.1 mg/kg to about 10 mg/kg or about 1 mg/kg to about 10 mg/kg per application. Administration can be daily, on alternating days, weekly, twice a month, monthly or more or less frequently, as necessary depending on the response to the disorder or condition and the subject's tolerance of the therapy. Maintenance dosages over a longer period of time, such as 4, 5, 6, 7, 8, 10 or 12 weeks or longer may be needed until a desired suppression of disorder symptoms occurs, and dosages may be adjusted as necessary. The progress of this therapy is easily monitored by conventional techniques and assays.

Specific dosages may be adjusted depending on conditions of disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs. Any of the above dosage forms containing effective amounts are well within the bounds of routine experimentation and therefore, well within the scope of the instant invention.

The anti-hepcidin antibody or specific binding agent is administered by any suitable means, either systemically or locally, including via parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral routes include intravenous, intraarterial, intraperitoneal, epidural, intrathecal administration. In addition, the specific binding agent or antibody is suitably administered by pulse infusion, particularly with declining doses of the specific binding agent or antibody. In some embodiments, the dosing is given by injections, e.g., intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Other administration methods are contemplated, including topical, particularly transdermal, transmucosal, rectal, oral or local administration e.g. through a catheter placed close to the desired site. In some embodiments, the specific binding agent or antibody described herein is administered intravenously in a physiological solution at a dose ranging between 0.01 mg/kg to 100 mg/kg at a frequency ranging from daily to weekly to monthly (e.g. every day, every other day, every third day, or 2, 3, 4, 5, or 6 times per week), or a dose ranging from 0.1 to 45 mg/kg, 0.1 to 15 mg/kg or 0.1 to 10 mg/kg at a frequency of 2 or 3 times per week, or up to 45 mg/kg once a month.

Diagnostic and Therapeutic Kits

In another related aspect, kits for treating a disorder associated with elevated hepcidin levels, or a hepcidin-related disorder, or a disorder of iron homeostasis, or a mammal with anemia, are also provided. In one embodiment, the kit includes (a) an anti-hepcidin antibody, and (b) an erythropoiesis stimulator, and optionally, iron. In another embodiment, the kit includes an anti-hepcidin antibody and a label attached to or packaged with the container, the label describing use of the anti-hepcidin antibody with an erythropoiesis stimulator. In yet another embodiment, the kit includes an erythropoiesis stimulator and a label attached to or packaged with the container, the label describing use of the erythropoiesis stimulator with an anti-hepcidin antibody. Also provided is the use of an anti-hepcidin antibody in preparation of a medicament for administration with an erythropoiesis stimulator, as well as use of an erythropoiesis stimulator in preparation of a medicament for administration with an anti-hepcidin antibody. In any of these kits or uses, the anti-hepcidin antibody and the erythropoiesis stimulator can be in separate vials or can be combined together in a single pharmaceutical composition. In yet another embodiment, an anti-hepcidin antibody or erythropoiesis stimulator, or both, can be combined with iron in a single pharmaceutical composition or can be in separate vials.

As a matter of convenience, an antibody disclosed herein can be provided in a kit, i.e., a packaged combination of reagents in predetermined amounts with instructions for performing the diagnostic assay. Where the antibody is labeled with an enzyme, the kit will include substrates and cofactors required by the enzyme (e.g., a substrate precursor which provides the detectable chromophore or fluorophore). In addition, other additives may be included such as stabilizers, buffers (e.g., a block buffer or lysis buffer) and the like. The relative amounts of the various reagents may be varied widely to provide for concentrations in solution of the reagents which

substantially optimize the sensitivity of the assay. Particularly, the reagents may be provided as dry powders, usually lyophilized, including excipients which on dissolution will provide a reagent solution having the appropriate concentration.

Also provided are diagnostic reagents and kits comprising one or more such reagents for use in a variety of diagnostic assays, including for example, immunoassays such as ELISA (sandwich-type or competitive format). In some embodiments, such kits may include at least a first peptide (optionally a properly folded mature hepcidin standard as described herein), or a first antibody or antigen binding fragment described herein, a functional fragment thereof, or a cocktail thereof, and means for signal generation. The kit's components may be pre-attached to a solid support, or may be applied to the surface of a solid support when the kit is used. In some embodiment, the signal generating means may come pre-associated with an antibody described herein or may require combination with one or more components, e.g., buffers, antibody-enzyme conjugates, enzyme substrates, or the like, prior to use. Kits may also include additional reagents, e.g., blocking reagents for reducing nonspecific binding to the solid phase surface, washing reagents, enzyme substrates, and the like. The solid phase surface may be in the form of a tube, a bead, a microtiter plate, a microsphere, or other materials suitable for immobilizing proteins, peptides, or polypeptides. In some embodiments, an enzyme that catalyzes the formation of a chemiluminescent or chromogenic product or the reduction of a chemiluminescent or chromogenic substrate is a component of the signal generating means. Such enzymes are well known in the art. Kits may comprise any of the capture agents and detection reagents described herein. Optionally the kit may also comprise instructions for carrying out the methods described herein.

Also provided is a kit comprising an anti-hepcidin antibody described herein and an erythropoiesis stimulator packaged in a container, such as a vial or bottle, and further comprising a label attached to or packaged with the container, the label describing the contents of the container and providing indications and/or instructions regarding use of the contents of the container to treat one or more disease states as described herein.

In one aspect, the kit is for treating a disorder associated with elevated hepcidin levels and comprises an anti-hepcidin antibody and an erythropoiesis stimulator. The kit may optionally further include iron for oral or parenteral, e.g. intravenous, administration. In another aspect, the kit comprises an anti-hepcidin antibody and a label attached to or packaged with the container describing use of the anti-hepcidin antibody with an erythropoiesis stimulator. In yet another aspect, the kit comprises an erythropoiesis stimulator and a label attached to or packaged with the container describing use of the erythropoiesis stimulator with an anti-hepcidin antibody. In certain embodiments, an anti-hepcidin antibody and an erythropoiesis stimulator, and optionally the iron, are in separate vials or are combined together in the same pharmaceutical composition. In yet another aspect, an anti-hepcidin antibody described herein is combined with iron in a single pharmaceutical composition. In yet another embodiment, the erythropoiesis stimulator is combined with iron in a single pharmaceutical composition.

As discussed above in the combination therapy section, concurrent administration of two therapeutic agents does not require that the agents be administered at the same time or by the same route, as long as there is an overlap in the time period during which the agents are exerting their therapeutic effect. Simultaneous or sequential administration is contemplated, as is administration on different days or weeks.

The therapeutic and diagnostic kits disclosed herein may also be prepared that comprise at least one of the antibody, peptide, antigen binding fragment, or polynucleotide disclosed herein and instructions for using the composition as a diagnostic reagent or therapeutic agent. Containers for use in such kits may typically comprise at least one vial, test tube, flask, bottle, syringe or other suitable container, into which one or more of the diagnostic and/or therapeutic composition(s) may be placed, and suitably aliquoted. Where a second therapeutic agent is also provided, the kit may also contain a second distinct container into which this second diagnostic and/or therapeutic composition may be placed. Alternatively, a plurality of compounds may be prepared in a single pharmaceutical composition, and may be packaged in a single container means, such as a vial, flask, syringe, bottle, or other suitable single container. The kits of the present invention will also typically include a means for containing the vial(s) in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vial(s) are retained. Where a radiolabel, chromogenic, fluorigenic, or other type of detectable label or detecting means is included within the kit, the labeling agent may be provided either in the same container as the diagnostic or therapeutic composition itself, or may alternatively be placed in a second distinct container means into which this second composition may be placed and suitably aliquoted. Alternatively, the detection reagent and the label may be prepared in a single container means, and in most cases, the kit will also typically include a means for containing the vial(s) in close confinement for commercial sale and/or convenient packaging and delivery.

A device or apparatus for carrying out the diagnostic or monitoring methods described herein is also provided. Such an apparatus may include a chamber or tube into which sample can be input, a fluid handling system optionally including valves or pumps to direct flow of the sample through the device, optionally filters to separate plasma or serum from blood, mixing chambers for the addition of capture agents or detection reagents, and optionally a detection device for detecting the amount of detectable label bound to the capture agent immunocomplex. The flow of sample may be passive (e.g., by capillary, hydrostatic, or other forces that do not require further manipulation of the device once sample is applied) or active (e.g., by application of force generated via mechanical pumps, electroosmotic pumps, centrifugal force, or increased air pressure), or by a combination of active and passive forces.

In related embodiments, also provided is a processor, a computer readable memory, and a routine stored on the computer readable memory and adapted to be executed on the processor to perform any of the methods described herein, and/or to generate as output the detected level of hepcidin and a threshold or range of threshold levels considered "normal", such that levels outside the "normal" range correlate with one or more of the conditions as described herein. In some embodiments, computer readable media containing programs or routines to perform similar functions are also provided. Examples of suitable computing systems, environments, and/or configurations include personal computers, server computers, hand-held or laptop devices, multiprocessor systems, microprocessor-based systems, set top boxes, programmable consumer electronics, network PCs, minicomputers, mainframe computers, distributed computing environments that include any of the above systems or devices, or any other systems known in the art.

Non-Therapeutic Uses for Anti-Hepcidin Antibodies

The antibodies disclosed herein may be used as affinity purification agents for target antigen or in diagnostic assays for target antigen, e.g., detecting its expression in specific cells, tissues, or serum. The antibodies may also be used for in vivo diagnostic assays. Generally, for these purposes the antibody is labeled with a radionuclide (such as ^{111}In, ^{99}Tc, ^{14}C, ^{131}I, ^{125}I, ^{3}H, ^{32}P or ^{35}S) so that the site can be localized using immunoscintiography.

The antibodies disclosed herein may be employed in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, such as ELISAs, and immunoprecipitation assays. Zola, Monoclonal Antibodies: A Manual of Techniques, pp. 147-158 (CRC Press, Inc. 1987). The antibodies may also be used for immunohistochemistry, to label cell samples using methods known in the art.

EXAMPLES

Example 1

Preparation of Anti-Human Hepcidin Monoclonal Antibodies

Monoclonal antibodies can be prepared by various procedures generally as described in copending U.S. patent application Ser. No. 12/022,515, incorporated by reference herein in its entirety. For example, Xenomouse™ IgG2κλ and IgG4κλ mice were immunized with KLH-conjugated human hepcidin (SEQ ID NO: 9) using standard methods. 23,040 IgG2 supernatants and 11,520 IgG4 supernatants were screened at a single concentration against biotinylated human hepcidin anchored to a plate. From this screen 617 IgG2 and 1013 IgG4 supernatants were tested for binding to both human and mouse biotinylated hepcidin using an antibody capture ELISA in which the amount of antibody captured was limited to minimize the effect of concentration differences between supernatants. Top-ranking samples (70 IgG2 and 110 IgG4) were further characterized in a bridging ELISA which measures solution-phase hepcidin-antibody binding over a range of antibody concentrations. This assay provided a relative affinity ranking of antibody binding.

Supernatants from each of the IgG2 and IgG4 panels were designated as follows: 1C9 (SEQ ID NOs: 107-116), 3B3 (SEQ ID NOs: 117-126), 4E1 (SEQ ID NOs: 127-136), 7A3 (SEQ ID NOs: 137-146), 9D12 (SEQ ID NOs: 147-156), 12B9 (SEQ ID NOs: 157-166), 15E1 (SEQ ID NOs: 167-176), 18D8 (SEQ ID NOs: 310-319), 19C1 (SEQ ID NOs: 320-329), 19D12 (SEQ ID NOs: 290-299), 19H6 (SEQ ID NOs: 300-309), 23F11 (SEQ ID NOs: 177-186), 26F11 (SEQ ID NOs: 187-196), 18B11 (SEQ ID NOs: 331-339), 19B8 (SEQ ID NOs: 341-349), 20E12 (SEQ ID NOs: 351-359), 22F12 (SEQ ID NOs: 361-369), 22H10 (SEQ ID NOs: 371-379), 23A11 (SEQ ID NOs: 381-389) and 24E4 (SEQ ID NOs: 391-399).

Generally, the binding affinities of these antibodies to human hepcidin were determined by BIAcore, which were then confirmed by KinExA if the K_D as estimated by BIAcore was below 100 pM. The binding affinity of antibody 18B11, however, was determined by KinExA without the BIAcore assay. The K_D for the lead antibodies were in the range of between 1 μM and more than 400 μM.

Relative species cross-reactivity and binding to Hepc20 (SEQ ID NO: 96) was determined by competition ELISA. 18B11 was observed to be cross-reactive with cynomolgus monkey hepcidin and not-significantly cross-reactive with mouse hepcidin. Antibody 18B11 competes with antibody 23F11 for binding to human hepcidin.

Example 2

Generation and Selection of Human Antibodies with Certain Pharmacokinetic Properties

2,522 hepcidin-specific antibodies were screened for differential binding profiles to human hepcidin at pH 7.4 and pH 6.0 by ELISA. 50 μL of Neutravidin (Pierce) at 8 μg/mL in 1×PBS was coated upon a Nunc Maxisorp 384-well plate, and incubated at 37° C. for 1 hr. After blocking the wells with 0.1% BSA/PBS/0.05% Tween20 for 1 hour at room temperature, plates were washed six times with PBS/0.05% Tween20. 25 μL of mono-biotinylated hepcidin at 50 ng/mL in 0.1% BSA/PBS/0.05% Tween20 was added to the 384-well plate, and incubated at room temperature for 1 hour. The plates were next washed six times with PBS/0.05% Tween20. Starting hepcidin antibody concentrations were normalized to 1 μg/mL for pH 5.5 and 6.0 conditions and to 100 ng/mL for pH 7.4 conditions. The hepcidin antibodies were serially diluted 3-fold in PBS/1% NFDM pH 7.4 and 4-fold in PBS/1% NFDM pH 6.0 and 5.5. The dilutions and titrations were performed in polypropylene 96-well dilution plates, and then were transferred in duplicate to a Neutravidin-coated 384-well plate. The biotinylated hepcidin and antibodies were incubated for 2 hours at room temperature. The plate was next washed six times with PBS/0.05% Tween20. 25 μL of goat anti-huIgG-horseradish peroxidase at a 1:7000 dilution in 0.1% BSA/PBS/0.05% Tween20 was next added to each well of the assay plate. The plate was finally washed six times in PBS/0.05% Tween20. Enhanced K-Blue 3,3',5,5'-Tetramethylbenzidine (TMB) Substrate (Neogen) was added and the reaction stopped using 1 M H_3PO_4 after 10 minutes of incubation at room temperature. The absorption was measured at 450 nm on a plate reader. Binding data were analyzed by non-linear regression analysis (sigmoidal dose-response, variable slope) to generate EC_{50} values using GraphPad Prism® software. From this screen 243 antibodies demonstrated a >2-fold difference in binding at pH 7.4 versus pH 6.0. The top 32 well supernatants were rescreened for a third time over a range of antibody dilutions at pH 7.4 and pH 6.0. Antibodies 18B11, 19B8, 20E12, 22C11, 22F12, 22H10, 23A11, 24E4 and 25H6 were selected for subcloning.

The binding affinities of these antibodies to human hepcidin were determined by KinExA and the off-rates were determined by BIAcore. At a 1:250 dilution, all of the antibodies tested demonstrated an about 10-fold reduction in affinity for hepcidin at pH 6 compared to pH 7.4.

Example 3

Engineering of Antibody with Differential pH Binding

Introduction of one or more histidine residues in the light and/or heavy variable region of an antibody can provide antibodies that exhibit differential pH binding to its antigen. Histidine is the amino acid most sensitive to pH shifts from 7.4 to 6.0, as the imidazole side chain of histidine has a pKa just over 6, varying higher or lower depending on the environment of the amino acid. This technique can be applied to any anti-hepcidin antibodies, including those described herein.

A crystal structure model of the Fv portion of the anti-hepcidin antibody 15E1 was prepared. Using this structure

model, all 62 CDR residues of antibody 15E1, using the Kabat definition, were selected for mutation, along with framework residues that were at least 10% exposed and within 4.5 Å of a CDR residue, resulting in an additional 31 residues for mutation. Additional positions were selected for mutation by visual inspection of the structure model for amino acids in proximity to the CDRs or selected framework residues. The encoding DNA was mutated to provide histidine mutations at single or multiple positions within the amino acid sequence. Mutations which produced some pH differential binding effect as single mutations can be combined as double, triple or more multiple mutations. The histidine mutations displayed collectively below were engineered at any one or more amino acids in which the "Mutants" sequence identifies a change to a histidine in the following diagram:

```
                                    11111111111              22
15E1 Light          SYELTQPPSVSVSPGQTATITCSGDKLGERYACWYQQRPGQSPVLVIYQD

15E1 Light Mutants  HHHLHHPPSVSVSPGQTATIHCHHHHHHHHHHHHWYQQRPGQSPHLVIHHH

                    22222                          3333333333
15E1 Light          SKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYFCQAWYSSTNVLFGG

15E1 Light Mutants  HHHHHHHHHRFHHHHHHHHATLTISGTQAMDEADYFCHHHHHHHHHHFGG

15E1 Light          GTKLTVLGQP

15E1 Light Mutants  GTKLTVLGQP

                                           11111             2
15E1 Heavy          QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAV

15E1 Heavy Mutants  QHQLVESGGGVVQPGRSLRLSCAASGHHFHHHHHHWVRQAPGKGLHHVAH

                    2222222222222222                          33
15E1 Heavy          IWYAESNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAQ

15E1 Heavy Mutants  HHHHHHHHHHHHHHHHHFHIHRHHSKNTLYLQMNSLHAEDTAVYYCARHH

                    333333333
15E1 Heavy          EGIAPDAFDIWGQGTMVTVSS

15E1 Heavy Mutants  HHHHHHHHHHHGQGTMVTVSS
```

Expression of Mutant Constructs

Mutations were introduced into wild-type constructs in vector pTT5 (heavy and light chains on separate vectors) using a Quickchange II kit (Stratagene #200523) and were transiently transfected into 293-6E cells (NRCC).

Light Chain Mutation
S1H
Y2H
E3H
T5H
Q6H
T21H
S23H
G24H
D25H
K26H
L27H
G28H
E29H
R30H
Y31H
A32H
C33H
V44H
Y48H

-continued

Q49H
D50H
S51H
K52H
R53H
P54H
S55H
G56H
I57H
P58H
E59H
S62H
G63H
S64H
N65H
S66H

-continued

G67H
N68H
T69H
Q88H
A89H
W90H
Y91H
S92H
S93H
T94H
N95H
V96H
L97H
Heavy Chain Mutation
V2H
F27H
T28H
S30H
S31H
Y32H
G33H
M34H
E46H
W47H
V50H
I51H
W52H

-continued

Y53H
A54H
E55H
S56H
N57H
K58H
Y59H
Y60H
A61H
D62H
S63H
V64H
K65H
G66H
R67H
T69H
S71H
D73H
N74H
R87H
A99H
Q100H
E101H
G102H
I103H
A104H
P105H
D106H
A107H
F108H
D109H
I110H
W111H

KinExA Solution Equilibrium Binding Analysis for Antibodies 15E1, 15E1 Variants and 18B11 to Binding to Human Hepc.

SA-Sepharose beads were pre-coated with biotinylated human hepcidin (SEQ ID NO: 9) and blocked with BSA according to manufacturer's instructions. Antibodies and hepcidin were diluted in PBS/0.1% BSA/0.05% NaN_3 buffer. Fixed concentrations of antibodies 15E1, 15E1 W52H, 15E1 A99H, 15E1 N521-1, 15E1 A107H and 18B11 were incubated with various concentrations of human hepcidin at room temperature for 8 hours before being run through the human hepcidin-coated beads. The amount of the bead-bound antibody was quantified by fluorescently (Cy5)-labeled goat anti-murine-IgG (H+L) antibody (Jackson Immuno Research, West Grove, Pa.). The binding signal is proportional to the concentration of free antibody at equilibrium. Dissociation equilibrium constant (K_D) was obtained from nonlinear regression of the competition curves using a dual-curve one-site homogeneous binding model (KinExATM Pro software). The results are set forth below in Table 3.

TABLE 3

Antibody	K_D	K_D range
18B11	7.4 nM	2-23.4 nM
15E1 (wild type)	37 pM	13-75 pM
15E1 A107H	31 pM	13-58 pM
15E1 A99H	>10 nM	N/A
15E1 N57H	3 nM	1.6-4.7 nM
15E1 W52H	1.7	5.8-16.5 nM

Differential pH binding of the antibodies listed above in Table 3 was then determined by ELISA. 50 μL of Neutravidin (Pierce) at 8 μg/mL in 1×PBS was coated upon a Nunc Maxisorp 384-well plate, and incubated at 37° C. for 1 hr. After blocking the wells with 0.1% BSA/PBS/0.05% Tween20 for 1 hour at room temperature, plates were washed six times with PBS/0.05% Tween20. 25 μL of mono-biotinylated hepcidin at 50 ng/mL in 0.1% BSA/PBS/0.05% Tween20 was added to the 384-well plate, and incubated at room temperature for 1 hour. The plates were next washed six times with PBS/0.05% Tween20. Starting hepcidin antibody concentrations were normalized to 1 μg/mL for pH 5.5 and 6.0 conditions and to 100 ng/mL for pH 7.4 conditions. The hepcidin antibodies were serially diluted 3-fold in PBS/1% NFDM pH 7.4 and 4-fold in PBS/1% NFDM pH 6.0 and 5.5. The dilutions and titrations were performed in polypropylene 96-well dilution plates, and then were transferred in duplicate to a Neutravidin-coated 384-well plate. The biotinylated hepcidin and antibodies were incubated for 2 hours at room temperature. The plate was next washed six times with PBS/0.05% Tween20. 25 μL it of goat anti-huIgG-horseradish peroxidase at a 1:7000 dilution in 0.1% BSA/PBS/0.05% Tween20 was next added to each well of the assay plate. The plate was finally washed six times in PBS/0.05% Tween20. Enhanced K-Blue 3,3',5,5'-Tetramethylbenzidine (TMB) Substrate (Neogen) was added and the reaction stopped using 1 M H_3PO_4 after 10 minutes of incubation at room temperature. The absorption was measured at 450 nm on a plate reader. Binding data were analyzed by non-linear regression analysis (sigmoidal dose-response, variable slope) to generate EC_{50} values using GraphPad Prism® software. Single mutations of wild type 15E1 that produced at least 1.5 fold increase in EC50 as the pH was lowered to 6.0 included $L_{27}H$ (light chain), A89H (light chain), W52H (heavy chain), N57H (heavy chain), A99H (heavy chain), and A107H (heavy chain). Double combinations of these mutants were made. Multiple mutants of wild type 15E1 with at least a 5.5 fold increase in EC50 as the pH was lowered to 6.0 included A107H (heavy chain)/A89H (light chain), A107H (heavy chain)/L27H (light chain), A107H (heavy chain)/N57H (heavy chain), and A107H (heavy chain)/A99H (heavy chain). Representative results are set forth in Table 4 below.

TABLE 4

	EC50 ng/mL		
Sample	pH 7.4	pH 6.0	pH 5.5
18B11	2.7	244.1	NC
15E1 (wild type)	2.3	2.3	2.3
15E1 L27H	4.5	6.5	8
15E1 A89H	5.4	10.6	12
15E1 W52H	4.5	5.8	17
15E1 N57H	1.8	4	3.2
15E1 A99H	4.1	10.7	29.1
15E1 A107H	2	3.6	3.7
15E1 N57H A107H	7.3	75.6	NC
15E1 A99H A107H	3.0	5.5	16.1
15E1 A107H A89H	6.0	34.7	NC
15E1 A107H L27H	4.3	19.3	316

Results indicated that antibody 18B11 demonstrated a 2-log lower apparent binding affinity and that 15E1 N57H A107H demonstrated a 1-log lower apparent binding affinity for hepcidin at pH 6.0 compared to pH 7.4.

Example 4

Off-Rate Binding Analysis for Human Antibody 18B11

Off-rate analysis of dissociation at different pHs was also performed. A slow off-rate is expected to predict increased binding interaction over a longer period of time, while a faster off-rate is expected to predict decreased binding interaction.

For example, a faster off-rate at lower pH is expected to predict greater release of antigen at lower pH. Solution equilibrium binding analysis was performed using BIAcore to study the off-rates of antibodies 1S1, 1S3, 2.7, 18B11, 23F11 and 26F11 with recombinant human hepcidin (SEQ ID NO: 9).

Preparation of Biacore Chip Surfaces

Immobilization of recombinant human hepcidin (rhuHepc) to a BIAcore sensor chip surface was performed according to manufacturer's instructions at a flow rate 10 μL/min of running buffer (DPBS: Dulbecco's Phosphate Buffer Salinel X, no CaCl or MgCl, with 0.005% Biacore surfactant P-20). The carboxylated matrix of the sensor chip was first activated with a 60 μL injection of a mixture containing 0.2 M EDC(N-ethyl-N-(dimethylamine-propyl)carbodiimide in water, from BIAcore) and 0.05M NHS (N-hydroxysuccinimide in water, from Biacore). 55 μL of recombinant human hepcidin (1 μg/ml in 10 mM Na-acetate pH4.0) was injected to immobilize onto the sensor chip. The excess reactive groups of the sensor chip were deactivated with an injection of 60 μL of ethanolamine (1.0M, from Biacore).

BIAcore Analysis

After rhuHepc was immobilized on the CM5 chip with low density, 50 nM of antibodies 1S1, 1S3, 2.7, 18B11, 23F11 and 26F11 were injected over and bound the rhuHepc surface at pH 7.4. Dissociation buffers with pH 7.4, pH6 and pH 5.5 were run over the bound surface. The dissociation curves were obtained. Results indicated that antibody 18B11 demonstrated a significant difference in off rate at pH 7.4 ($>1\times 10^{-2}$) compared to pH 5.5. The other antibodies tested did not demonstrate a significant difference in off rate at pH 7.4, 6.0 or 5.5. See FIG. **1**.

Example 5

In Vitro Hepcidin Activity in an Iron-Responsive B-Lactamase Assay can be Neutralized by Anti-Hepcidin Antibodies

Hepcidin causes ferroportin to be internalized and removed from the cell surface, thus inhibiting release of iron and raising intracellular iron concentrations. The effect of anti-human hepcidin antibodies on this hepcidin-mediated iron sequestration was evaluated in vitro. A 293 cell line containing a doxycycline-inducible ferroportin (Fpn) expression construct as well as a beta-lactamase (BLA) expression construct containing one copy of the 5' iron response element (IRE) from ferritin having the following nucleotide sequence:

(SEQ ID NO: 103)

```
tcggccccgcctcctgccaccgcagattggccgctagccctccccgagc

gccctgcctccgagggccggcgcaccataaaagaagccgccctagccac

gtcccctcgcagttcggcggtcccgcgggtctgtctcttgcttcaacag

tgtttggacggaacagatccggggactctcttccagcctccgaccgccc

tccgatttcctctccgcttgcaacctccgggaccatcttctcggccatc

tcctgcttctgggacctgccagcaccgtttttgtggttagctccttctt

gccaacc
```

that regulates mRNA translation was constructed. These 293/Fpn/BLA cells, taken from a 70-80% confluent culture, were plated at 2.8×10^5 cells/mL in DMEM (Invitrogen Cat# 11965) 5% FBS (Invitrogen. Cat# 10099-141) PSQ (Invitrogen Cat# 10378-016), 90 μL/well (25,000 cells/well) in Bio-Coat Poly-D Lysine coated plates (Becton-Dickinson Cat# 35-6640) and incubated at 37C with 5% CO_2. At the end of the same day, a solution of assay medium (DMEM 5% FBS PSQ) with 100 ug/mL doxycycline was made, 10 μL/well of it added to the plate, and the plate incubated overnight or for at least 20 hours. The next day, media was removed from the wells and replaced with premade mixes of DMEM 5% FBS PSQ, 2.5 μg/mL ferric citrate, 50 ng/mL synthetic human hepcidin and serial dilutions of the antibodies (24E4, 23F11, 18B11, 2.7, 2.41, and Ab43), all prepared in a 96-well polypropylene deep-well block plate immediately before addition to the assay plate. Mixtures were added at 100 μL/well and incubated overnight at 37C, 5% CO_2 in a cell culture incubator. Plates were then removed from the incubator and equilibrated to room temperature for 10 minutes before adding 20 μL/well of the prepared Invitrogen GeneBlazer CCF4 A/M development reagent (Invitrogen Kit# K1085) and incubating for 90 minutes in the dark. Development reagent was also added to 16 wells of a control assay plate without cells containing 100 μL assay medium (DMEM 5% FBS PSQ) and incubated for the same time. Blue & Green fluorescence signals were then read on an Envision Multilabel Reader (Perkin-Elmer Inc.) by exciting at 409 nm and reading emissions at 447 nm (blue) and 520 nm (green). The results are depicted in FIGS. **2** and **3**. It was determined that mAb 43, 2.7, 2.41, 18B11, 23F11, 24E4 decreased intracellular concentration of iron at an EC_{50} of 1.380×10^{-8}, 1.700×10^{-8}, 1.636×10^{-8}, 2.0×10^{-8},2.3×10^{-9} and 5.0×10^{-9}, respectively.

Example 6

Anti-Hepcidin Antibodies Neutralize Human Hepcidin in Mice

Activity of anti-human hepcidin antibodies was evaluated in vivo in mice that were administered human hepcidin in an amount sufficient to generate a hypoferremic response. On day 0, female C57BL/6 mice were injected subcutaneously with a murine monoclonal antibody (Ab2.7) directed against human hepcidin. Control mice received murine IgG1 as an isotypic control. At day 3, the mice received a single intraperitoneal injection of 25 μg *E. coli*-derived recombinant human Hepcidin (rhHepc). Serum iron levels were analyzed two hours later. Control animals treated with saline had normal serum iron levels, while animals treated with hepcidin and an isotype control antibody showed hypoferremia. Results are set forth in FIG. **4**B. Both 1 mg and 0.5 mg of mAb2.7 provided statistically significant protection from the hypoferremic response. Although a reduction in hypoferremia was observed at the 0.25 mg dose of Ab 2.7, the lower doses (0.25 and 0.1 mg) were defined as non-neutralizing doses. Statistics represent ANOVA with a Dunnett's post-hoc test comparing all groups against the saline control.

Example 7

Antibody Neutralization of AAV-Delivered Hepcidin Restores Normal Early Red Blood Cell Characteristics

AAV-mediated human hepcidin expression in mice produces a microcytic, hypochromic anemia consistent with iron deprivation. The activity of anti-human hepcidin antibodies was evaluated in vivo in these mice overexpressing human hepcidin. Male C57B1/6 mice were injected with AAV (1.5×10^{12} particles/mouse, I.V.) containing expression cassettes

for either human hepcidin or beta-galactosidase (β-gal) as a negative control. The mice were left for two weeks to allow constitutive production of huHepc before being treated with 1 mg/mouse of Ab 2.7 or isotype control (muIgG1) at various dosing frequencies (1×, 2× and 4× per week) as shown in FIG. **5**A. Blood was drawn on the fifth day for serum iron levels and determination of early red blood cell (reticulocyte) characteristics (reticulocyte count, reticulocyte hemoglobin content (CHr), and reticulocyte mean cell volume (Retic. MCV))

Results are set forth in FIGS. **5**B-**5**E. Serum iron levels were restored to normal in mice receiving 4× dosing of Ab2.7 but not isotype control. All mice receiving Ab2.7 showed increased reticulocyte production. The reticulocyte hemoglobin content (CHr) was normal in mice given the 4× and 2× dosing of Ab 2.7, but hypochromicity is still seen in groups with 1× dosing, or the isotype control group. Treatment with Ab2.7 at the 4× and 2× dose restored normal volume to reticulocytes (Retic. MCV) but microcytosis was still present in the 1× and isotype control groups. Statistical comparisons to β-gal injected animals with isotype control treatment were determined to look for restoration of normal red cell characteristics (ANOVA with Dunnett's post-hoc test).

In another experiment, the activity of anti-human hepcidin antibodies 1S1, 18B11 and 24E4 was evaluated in vivo in mice overexpressing human hepcidin. C57B1/6 mice (4 weeks of age) were obtained from Charles River Laboratories. On Week 0, mice (n=5 per group) were injected via the tail vein with AAV containing human hepcidin (hHepc) or green fluorescence protein (GFP) as an expression control. Mice were maintained for 2 weeks after viral introduction to allow for protein expression before treatment with antibody. Mice were treated with either 1 mg or 0.5 mg of each antibody 1S1, 18B11 and 24E4 (subcutaneous injection, 0.2 ml/mouse in PBS) on Days 14 and 16 following viral introduction. Blood was collected on Day 18, and response to antibody administration was measured as a change in reticulocyte characteristics (reticulocyte cellular hemoglobin content) using an ADVIA 2120 Hematology Analyzer (Bayer Corporation, Tarrytown, N.Y.). Total serum hepcidin levels (free and bound) were measured by ELISA to determine the degree of complex formation. All results were expressed as the mean±standard error of the mean. ANOVA and a Dunnett's post test using Graphpad Prism software v4.0 (San Diego, Calif.) assessed statistical significance of differences (* denotes $p<0.05$, and ** denotes $p<0.01$ compared to AAV-hHepc+isotype control group).

After 18 days, the reticulocytes in the AAV-hHepc+isotype treated control mice had reduced hemoglobin content (CHr), rendering them hypochromic. Animals treated with anti-hepcidin antibodies 1S1, 18B11 or 24E4 at either 1 mg or 0.5 mg/mouse had normal CHr values as compared to AAV-GFP control mice, indicating that these antibodies are efficacious in this model in restoring normal early red cell characteristics. See FIGS. **6**A and **6**B.

Results indicated that mice treated with the 1 mg dose of antibody 18B11 had a 10-fold reduction in total serum hepcidin compared to animals treated with antibody 1S1 or antibody 24E4 (FIG. **7**A). Similar results were obtained at the 0.5 mg/mouse dose (FIG. **7**B). The markedly reduced amount of total hepcidin seen with antibody 18B11, is consistent with hepcidin clearance through endosomes.

Example 8

Viral Hepcidin Over-Expression Results in Hypo-Responsiveness to Erythropoietin

The following Example investigated the role of hepcidin and anti-hepcidin antibodies in erythropoietin hypo-responsive mice.

Titration of AAV-mediated human hepcidin expression in mice causes an increase in serum hepcidin levels and dose-dependent hypoferremia, as shown in FIG. **8**. Doses of AAV-human hepcidin were selected that gave an erythropoietin resistant phenotype and expressed levels of hepcidin in a similar range to that detected in cancer patient samples in previous studies (as described in co-pending co-owned U.S. patent application Ser. No. 11/880,313 and International Publication No. WO 2008/011158, the disclosures of which are incorporated herein by reference in their entirety). Male C57BL/6 mice were injected with AAV expressing human hepcidin or GFP as an expression control (n=4 per group). The mice were injected through the tail vein (human hepcidin, from 1×10^{12} to 3×10^{12} particles/mouse; GFP 3×10^{12} particles/mouse). Protein expression was allowed to develop for two weeks prior to harvest. At two weeks, serum was collected from the mice and iron and hepcidin levels were determined. Results are reported in FIG. **8**.

In order to evaluate hepcidin's effect on erythropoietin resistance, male C57BL/6 mice were injected with AAV (3×10^{12} particles/mouse, hepatic portal vein delivery) containing expression cassettes for either human hepcidin or GFP as a negative control (n=5 per group). The mice were left for three weeks to allow constitutive production of human hepcidin, and then bled to determine baseline hemoglobin (Hb) levels. The mice were treated with darbepoetin alfa (100 μkg/mouse) or saline as a negative control at four weeks. At five weeks, hemoglobin levels were again measured. Results are shown in FIG. **9**. Mice over-expressing human hepcidin are resistant to high doses of darbepoetin alfa. Resistance to darbepoetin alfa demonstrates that elevated hepcidin levels are sufficient to cause hypo-responsiveness to erythropoetin.

Example 9

Combination Therapy with Hepcidin Antibody and an Erythropoiesis Stimulator in a Viral Hepcidin Over-Expression Model

Treating mice that possessed an erythropoetin resistant phenotype with an anti-hepcidin antibody restored responsiveness to treatment with darbepoetin alfa. Male C57BL/6 mice were injected with AAV (5×10^{12} particles/mouse, I.V.) containing genes coding for either human hepcidin or GFP as an expression control (n=5 per group). After allowing two weeks to establish constitutive protein expression, mice were bled to determine baseline hemoglobin (Hb) levels, then treated with Ab 2.7 (1 mg/mouse) or isotype control at various dose frequencies. On the day after the first dose, they were treated with darbepoetin alfa (100 μg/kg, subcutaneous). A schematic of the dosing schedule appears in FIG. **10**A.

Neutralization of hepcidin restores responsiveness to darbepoetin alfa. Monday-Wednesday-Friday dosing of the antibody led to a partial response to darbepoetin alfa treatment as measured by an increase in Hb levels; a cohort with the same antibody dosing without darbepoetin alfa treatment showed no rise in Hb levels. (See FIG. **10**B) A maximal response to darbepoetin alfa was achieved in mice receiving daily (Monday through Friday) dosing of Ab 2.7. (See FIG. **10**C) Two and three doses of antibody in combination with darbepoetin alfa treatment led to a partial response, as measured by Hb levels. (See FIG. **10**D) Antibody dose and proximity of antibody dose to darbepoetin alfa treatment affected overall Hb response to anti-hepcidin antibody treatment, as shown in FIG. **10**E (results varying from the control where $p<0.01$ by ANOVA with Dunnett's post-hoc test are noted with double

asterisks). Thus, antibody-mediated neutralization of hepcidin was shown to be an effective treatment for anemia caused by elevated hepcidin levels.

Example 10

Combination Therapy with an Anti-Hepicin Antibody and Erythropoiesis Stimulator in a Mouse Model of Inflammatory Anemia

Combination therapy with an anti-hepcidin antibody and an erythropoiesis stimulator was also evaluated in a murine inflammatory anemia model as follows.

Mice were generated such that murine hepcidin 1 was knocked out and replaced with human hepcidin. Female mice, both homozygous for human hepcidin expression and wild-type littermate controls, were injected with *Brucella abortus* (2×10^8 particles/mouse, I.P.) on day 0 and then bled on day 6 to assess hemoglobin levels. The mice were then treated with either Antibody 2.7 or an isotype control antibody (1 mg/mouse/day) on days 6 through 9. Darbepoetin alfa was administered (100 μg/kg/mouse) on day 7, and Hb levels evaluated on day 13. A schematic of the protocol is shown in FIG. **11**A.

Wild-type control mice which still possessed the mouse hepcidin 1 gene did not respond to darbepoetin alfa either with or without Ab 2.7. (See FIG. **11**B) Human knock-in mice treated with Antibody 2.7 exhibited a restored responsiveness to darbepoetin alfa treatment, as shown by the maintenance of stable hemoglobin levels. (See FIG. **11**C).

These results demonstrate that anti-hepcidin antibodies can be used to neutralize hepcidin under conditions of hepcidin excess and restore responsiveness to erythropoietic agents in hepcidin-mediated anemias such as the anemia of inflammation.

Example 11

Measurement of Hepcidin Level in Patients

The level of hepcidin in human patients was measured by spectrometry techniques as previously described in co-pending co-owned U.S. patent application Ser. No. 11/880,313 and International Publication No. WO 2008/011158, the disclosures of each of these applications are incorporated herein by reference in their entirety. The method is reproduced below.

Samples from patients suffering from anemia of cancer (obtained from ProteoGenex) or volunteers (control) were collected. 100 μL of each sample, serum blanks and calibration standards consisting of seven non-zero concentrations in duplicates (10, 25, 50, 100, 250, 500, 1000 ng/mL) were extracted by SPE using an Oasis HLB mElution 96-well plate (Waters, Milford, Mass.). Washing solvent was 30% methanol/water with a pH of about 10 adjusted with ammonium hydroxide. Elution solvent was 90% methanol/water solution with a pH of about 5 adjusted with acetic acid. The SPE plate was activated with 500 μL methanol and conditioned with 500 μL water, then 100 μl, serum sample and 200 μL internal standard were loaded onto the elution plate, washed with 350 μL water and 350 μL washing solvent. Elution was done using 100 μL elution solvent and diluted with 100 μL water. The resulting 200 μL eluate was analyzed by LC-MS/MS.

20 μl of each extracted sample was injected onto a Polaris C18A, 5 μm HPLC column (2.1×50 mm, Varian). The LC flow rate was set to 300 μl/min. The HPLC mobile phase A was 5:95 methanol/water, and mobile phase B was 95:5 methanol/water, both containing 0.1% formic acid. The gradient conditions were set as follows: 0-0.1 min, isocratic 2% B/98% A; 2% B to 95% B at 0.1-4.5 min; 95% B at 4.5-4.9 min; 95% B to 2% B at 4.9-5.0 min; 5.0-6.0 min, isocratic 2% B.

A Sciex API4000 triple quadrupole mass spectrometer from Applied Biosystems (Foster City, Calif.) with Turbo ESI source was used for hepcidin detection in MRM mode with ion transition of m/z 930.60 to m/z 110.15. Quantification was achieved by comparing the ratio of the LC peak areas of the hepcidin and the internal standard to the ratios obtained from a series of standards where the amounts of hepcidin and internal standard were known.

This experiment allowed for the determination of the serum levels of hepcidin in a control population presumed to contain a large number of healthy individuals as well as the serum level of hepcidin from patients suffering anemia of cancers (AoC). The results are shown in FIG. **12**.

Each patient's sample was then analyzed for other iron index concentrations to determine whether a patient had inflammation or iron deficiency anemia (FIG. **13**). The parameters were measured as follows: serum iron, UIBC, ferritin, and CRP were measured on an Olympus AU400 clinical laboratory analyzer using standard procedures; sTfR was measured using a standard ELISA method (R&D systems).

As described in copending U.S. patent application Ser. No. 12/022,515, incorporated by reference herein in its entirety, prohepcidin levels measured using the DRG prohepcidin ELISA kit, however, do not correlate with the mature hepcidin levels of the patients, nor do prohepcidin levels correlate with the inflammatory status of patients. Hepcidin, but not prohepcidin, shows a relationship with CRP in anemia of cancer patients, and can therefore be used as a marker of inflammation.

Distinguishing the anemia of inflammation (AI) from iron deficiency anemia (IDA) and mixed anemia (components of both AI and IDA) is complicated since most of the commonly used lab parameters are influenced by acute phase responses. A ratio utilizing soluble transferrin receptor (sTfR) and ferritin (Ft) values has been described in the literature as a means to provide a more accurate diagnosis. See Punnonen et al., *Blood*, 89:1052-57, 1997. Anemia of inflammation is characterized by a low sTfR/log Ft quotient (values less than one), while a high ratio is indicative of IDA. Hence, the sTfR/log Ft ratio may serve as an accurate predictor of the three conditions when combined with an inflammatory marker to aid diagnosis of mixed anemia from absolute IDA.

Hepcidin levels are strongly related to sTfR/log Ft levels in AoC patients ($r=-0.6407$; $P<0.0001$), thus aiding patient diagnosis.

Using a decision tree combining CRP as a marker of inflammation and sTfR/logFt, anemia of cancer patients could be sub-divided into those with AI, with mixed anemia, with IDA and with an anemia of unknown origin, designated 'other' (FIG. **14**A). Patients with elevated hepcidin levels were all observed to have either AI or a mixed anemia. (FIG. **15**). Patients with low or absent hepcidin levels were observed to have either IDA or anemia of unknown origin. Hepcidin levels, as measured by the antibody-based immunoassay methods described in copending U.S. patent application Ser. No. 12/022,515, incorporated by reference herein in its entirety, or the mass spectrometry-based method quantitation method described in co-pending co-owned U.S. patent application Ser. No. 11/880,313 and International Publication No. WO 2008/011158, the disclosures of which are incorporated

herein by reference in their entirety, and discussed in detail above, can be used to diagnose inflammatory anemia.

Example 12

Monoclonal Antibodies in a Sandwich Immunoassay for Hepcidin

The following Example describes a sandwich immunoassay to determine hepcidin levels in a sample.

Using Biacore analysis, a surface coated with antibody 1S1 was tested for the concurrent binding of hepcidin and another antibody (FIG. **16**). Immobilization of anti-Hepc antibody 1S1 to the sensor chip surface was performed according to manufacturer's instructions using a continuous flow of 0.005% P-20/PBS buffer. Briefly, carboxyl groups on the sensor chip surfaces were activated by injecting 60 μL of a mixture containing 0.2 M N-ethyl-N'-(dimethylaminopropyl)carbodiimide (EDC) and 0.05 M N-hydroxysuccinimide (NHS). This was followed by injecting 1S1 diluted in 10 mM acetate, pH 4.0 at concentrations between 20 μg/mL. Excess reactive groups on the surfaces were deactivated by injecting 60 μL of 1 M ethanolamine. Final immobilized levels were 5,000-6,000 resonance units (RU) for the Ab 1S1 surface. A blank, mock-coupled reference surface was also prepared on the sensor chip. 20 nM *E. coli*-derived human hepcidin was injected over and bound to the 1S1 antibody surface. Then 50 nM antibody 2.7, 23F11, 26F11, and 1S1 were injected over the hepcidin/1S1 surface. After the antibody injection, the surfaces were regenerated by injecting 10 mM HCl pH 2.0.

There was a high selectivity of binding in the form of complexes. The murine antibody 2.7, which was used in the competitive assay above, was not able to form a sandwich pair with 1S1, and 26F11 showed markedly lower ability to bind to hepcidin concurrently with 1S1 than did 23F11.

When 1S1 and 23F11 were assembled into a sandwich ELISA format, the sensitivity of the immunoassay for detecting hepcidin levels was improved by 50-fold. As shown in FIG. **17**, the assay proved capable of measuring levels of hepcidin in normal sera after a 50-fold pre-dilution step. The axis represents the hepcidin levels pre-dilution.

Example 13

Competitive Binding Assay

The following Example describes a competitive binding assay to determine hepcidin levels. In one protocol, unlabeled hepcidin present in serum competes with biotinylated hepcidin for binding to an anti-hepcidin antibody (e.g., Antibody 2.7).

Hepcidin levels were determined using hepcidin standards of varying concentrations (from 1.4-300 ng/ml) spiked into buffer (5% BSA:I-block), rabbit serum, or pooled human serum. Hepcidin was added to equal volumes of 40 ng/mL of Ab2.7 and incubated for 120 minutes. 25 μl/well of mixed solution was added to Black half area plates coated with 1-2 μg/mL GxM capture antibody. 25 μL/well of biotinylated hepcidin was added at 0.25 nM. The plate was covered with plate film sealer and incubated at room temperature (25° C.) on a plate shaker at around <200 RPM for around 60 minutes. The plate was washed and then 50 μL/well of Poly horseradish peroxidase amplification reagent at 1:2000 was added. The plate was allowed to sit for 30 minutes and was then washed with a plate washer using PBS or KPL buffer 6 times. The plate was patted dry and a luminescent substrate (Femto or Pico) was quickly added. The plate was read with luminometer (ex: Lmax 340) for 1 second using Femto or Pico Substrate. Results indicated that hepcidin was measurable at a concentration range of 1-100 ng/ml in both the rabbit serum and buffer. (FIG. **18**).

Pooled human serum appeared to have an existing hepcidin level of greater than 20 ng/ml. It was determined that the levels of hepcidin varied substantially in human sera, over the range of 1-30 ng/ml for various randomly selected sera (FIG. **19**).

Using hepcidin standards in rabbit serum determined above, 24 random sera from normal human subjects was tested. The hepcidin levels varied from undetectable to over 50 ng/ml. See FIG. **20**. These values were at variance with the results from the levels of hepcidin measured through the mass spectrometry-based quantitation method described in co-pending co-owned U.S. patent application Ser. No. 11/880,313 and International Publication No. WO 2008/011158, the disclosures of which are incorporated herein by reference in their entirety, which generally gave much lower values.

Example 14

Pharmacokinetic Study of Antibody Following Single Dose of Antibody-Hepcidin Complex

C57 BL/6 mice were pre-dosed with either the control antibody or antibodies 1S1 or 18B11 on Day 0 as a single intraperitoneal injection at a dose of 1 mg/mouse to ensure that the antibody concentration was above the antibody K_D. On Day 1, the mice were dosed with an antibody-hepcidin complex (i.e., either 1S1-hepcidin complex or 18B11-hepcidin complex). Urine samples for determination of hepcidin concentrations were collected prior to hepcidin administration and at 1 hour, 24 and 96 hours antibody-hepcidin complex administration. The results are set forth in Table 5 below.

TABLE 5

Time (hours)	1S1 Hepcidin Concentration	18B11 Hepcidin Concentration
1	Not detectable	20 ng/mL
24	Not detectable	Not detectable
96	Not detectable	Not detectable

Serum samples for determination of serum antibody and serum hepcidin concentrations were collected at 5 minutes, 1 hour, 24 hours, 96 hours, 168 hours, 264 hours and 336 hours after administration of the antibody-hepcidin complex. Serum antibody and hepcidin concentrations were calculated by ELISA and the results are set forth in FIGS. **21** and **22**, respectively. Results indicated that the concentration of serum hepcidin at the 5-minute timepoint in mice that received the 18B11-hepcidin complex was lower compared to the 1S1-hepcidin complex. Interestingly, hepcidin was not detectable after 24 hours in mice that received the 18B11-hepcidin complex, while mice treated with the 1S1-hepcidin complex still had detectable levels of serum hepcidin at 168 hours.

Example 15

Pharmacokinetic Study of Antibodies Following Single Dose of Free Hepcidin to Mice

C57 BL/6 mice were pre-dosed with either the control antibody or antibodies 1S1 or 18B11 on Day 0 as a single

intraperitoneal injection at a dose of 1 mg/mouse. On Day 1, the mice were predosed with the antibodies as a single intravenous injection at a dose of 1 mg/mouse. On Day 4, human hepcidin (3.72 μg/mouse) was administered to the mice by intravenous injection. Urine samples for determination of hepcidin concentrations were collected prior to hepcidin administration and at 1 hour, 6 hours and 24 hours post-hepcidin administration. Results indicated that hepcidin was not detected in mice pre-dosed with either 1S1 or 18B11. See FIG. **23**.

Serum samples for determination of antibody 1S1 or 18B11 and hepcidin concentrations were collected at 5 minutes, 1 hour, 24 hours, 96 hours, 168 hours, 264 hours and 336 hours after administration of the hepcidin. Serum antibody and hepcidin concentrations were calculated by ELISA and the results are set forth in FIGS. **24** and **25**, respectively. Results indicated that antibody 18B11 cleared all detectable serum hepcidin by 24 hours, while hepcidin levels stabilized in mice treated with antibody 1S1.

Example 16

Detection of Hepcidin Intracellular Accumulation by Antibodies Contacted with Cells Expressing FCRN

FcRn is the salvage receptor involved in recycling antibodies by rescuing them from endosomal degradation. This Example examined the effect of antibodies on relative levels of intracellular hepcidin compared to total hepcidin, providing an indication of the internalization and subsequent degradation of hepcidin by cells expressing FcRn. Alexa-647 labeled 1S1 or 18B11 antibodies were complexed with excess of biotinylated-hepcidin by incubation for 10 minutes at room temperature. Free hepcidin was removed using spin-columns. 293T/FcRn cells were incubated with the antibody-hepcidin complexes for 6 hours at 37° C., 5% CO_2 in 0% FBS medium. At the end of the incubation cells were harvested in cold FACs buffer (PBS 2% FBS). Cells from each group were either fixed only (detection of extracellular hepcidin) or fixed and permeabilized (detection of total hepcidin) using R&D's CytoFix and CytoPerm reagents. All samples were stained with SA-PE and read on FACS. Results indicated that antibody 18B11 caused greater intracellular accumulation of hepcidin compared to antibody 1S1. See FIG. **26**. Of the total hepcidin detected in association with cells contacted with 1S1, all of the hepcidin was extracellular. Of the total hepcidin detected in association with cells contacted with 181311, only about one-third of the hepcidin was extracellular and the remainder was intracellular.

For the sake of completeness of disclosure, all patent documents and literature articles cited herein are expressly incorporated in this specification by reference in their entireties.

The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Since modifications of the described embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art, the invention should be construed broadly to include all variations within the scope of the appended claims and equivalents thereof.

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Gly Trp Ile Asn Thr Tyr Ser Gly Val Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys

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85 90 95

Ala Ser Leu Trp Tyr Tyr Gly Arg Ala Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> SEQ ID NO 16
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

Arg Ala Ser Glu Ser Val Asp Ser Tyr Gly Asn Ser Phe Met His
1 5 10 15

<210> SEQ ID NO 17
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Leu Ala Ser Asn Leu Glu Ser
1 5

<210> SEQ ID NO 18
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Gln Gln Asn Asn Glu Asp Arg Thr
1 5

<210> SEQ ID NO 19
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

Thr Tyr Gly Met Ser
1 5

<210> SEQ ID NO 20
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

Trp Ile Asn Thr Tyr Ser Gly Val Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 21
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Leu Trp Tyr Tyr Gly Arg Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 22

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<400> SEQUENCE: 22

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<210> SEQ ID NO 23

<400> SEQUENCE: 23

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<210> SEQ ID NO 24
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atatcctgca gagccagtga aagtgttgat agttatggca atagttttat gcactggtac 120

cagcagaaac caggacagcc acccaaactc ctcatctatc gtgcatccaa cctagaatct 180

gggatccctg ccaggttcag tggcagtggg tctaggacag acttcaccct caccattaat 240

cctgtggagg ctgatgatgt tgcaacctat tactgtcacc aaagtaatga ggagtacacg 300

ttcggagggg ggaccaagct ggaaataaaa 330

<210> SEQ ID NO 25
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

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

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Ser Tyr
20 25 30

Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

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

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

Glu Glu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 26
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

cagatccagt tggtacagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggta taccttcaca acctatggaa tgagctgggt gaaacaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaatacct actctggagt gccaacatat 180

gctgatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatca acaacctcaa aaatgaggac acggctacat atttctgtgg aagagaccac 300

tactacgggg aggttgctta ctggggccaa gggactctgg tcactgtctc tgca 354

<210> SEQ ID NO 27
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

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

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

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

Gly Trp Ile Asn Thr Tyr Ser Gly Val Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

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

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

Leu Val Thr Val Ser Ala
115

<210> SEQ ID NO 28
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Arg Ala Ser Glu Ser Val Asp Ser Tyr Gly Asn Ser Phe Met His
1 5 10 15

<210> SEQ ID NO 29
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Arg Ala Ser Asn Leu Glu Ser
1 5

<210> SEQ ID NO 30
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

His Gln Ser Asn Glu Glu Tyr Thr
1 5

<210> SEQ ID NO 31
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Thr Tyr Gly Met Ser
1 5

<210> SEQ ID NO 32

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<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

Trp Ile Asn Thr Tyr Ser Gly Val Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 33
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Asp His Tyr Tyr Gly Glu Val Ala Tyr
1 5

<210> SEQ ID NO 34

<400> SEQUENCE: 34

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<210> SEQ ID NO 35

<400> SEQUENCE: 35

000

<210> SEQ ID NO 36
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atatcctgca gagccagtga aagtgttgat agttttggca atagttttat gcactggtac 120

cagctgaaac caggacagcc acccaaactc ctcatctatc gtgcatccaa cctagaatct 180

gggatccctg ccaggttcag tggcagtggg tctaggacag acttcaccct caccattaat 240

cctgtggagg ctgatgatgt tgcaatttat tactgtcagc aaagtaatga ggagtacacg 300

ttcggagggg ggaccaagct ggaaataaaa 330

<210> SEQ ID NO 37
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

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

Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Ser Phe
20 25 30

Gly Asn Ser Phe Met His Trp Tyr Gln Leu Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser Gly Ile Pro Ala
50 55 60

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

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Pro Val Glu Ala Asp Asp Val Ala Ile Tyr Tyr Cys Gln Gln Ser Asn
85 90 95

Glu Glu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 38
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

cagatccagt tggtacagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctgggta taccttcaca acctatggaa tgagctgggt gaaacaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacacct cctctggagt gccaacatat 180

gctgatgact tcatgggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatca acaacctcaa aaatgaggac acggctacgt atttctgtgc aagagaccgc 300

tactacgggg aggttgctta ctggggccaa gggactctgg tcaccgtctc tgca 354

<210> SEQ ID NO 39
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

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

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

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

Gly Trp Ile Asn Thr Ser Ser Gly Val Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Met Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

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

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

Leu Val Thr Val Ser Ala
115

<210> SEQ ID NO 40
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Arg Ala Ser Glu Ser Val Asp Ser Phe Gly Asn Ser Phe Met His
1 5 10 15

<210> SEQ ID NO 41
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Arg Ala Ser Asn Leu Glu Ser
1 5

<210> SEQ ID NO 42
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Gln Gln Ser Asn Glu Glu Tyr Thr
1 5

<210> SEQ ID NO 43
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Thr Tyr Gly Met Ser
1 5

<210> SEQ ID NO 44
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Trp Ile Asn Thr Ser Ser Gly Val Pro Thr Tyr Ala Asp Asp Phe Met
1 5 10 15

Gly

<210> SEQ ID NO 45
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Asp Arg Tyr Tyr Gly Glu Val Ala Tyr
1 5

<210> SEQ ID NO 46

<400> SEQUENCE: 46

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<210> SEQ ID NO 47

<400> SEQUENCE: 47

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<210> SEQ ID NO 48
<211> LENGTH: 317
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

acatccagat gacccagtct ccttcactcc tgtcagcatc tgtgggagac agagtcactc 60

tcagctgcaa agcaagtcag aatatttaca agtacttaaa ctggtatcag caaaagcttg 120

gagaagctcc caaactcctg atatattata caaacagttt gcaaacgggc atcccatcaa 180

ggttcagtgg cagtggatct ggtacagatt tcacacttac catcagcagc ctgcagcctg 240

aagatgttgc cacatattac tgctatcagt ataacagtgg gcccacgttt ggagctggga 300

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ccaagctgga actgaaa 317

<210> SEQ ID NO 49
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

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

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

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

Tyr Tyr Thr Asn Ser Leu Gln Thr Gly Ile 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 Val Ala Thr Tyr Tyr Cys Tyr Gln Tyr Asn Ser Gly Pro Thr
85 90 95

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> SEQ ID NO 50
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

caggttactc tgaaagagtc tggccctggg atattgcagc cttcccagac cctcagtctg 60

acttgctctt tctctgggtt ttcactgagc acttctggta tatgtgtgag ctggattcgt 120

cagccttcag ggaagggtct ggagtggctg gcaactattt gttgggagga tagtaagggc 180

tacaaccctt ctctgaagaa ccggctcaca atctccaagg acacctccaa caaccaagca 240

ttcctcaaga tcaccagtgt ggacactgca gataccgcca tatactactg tgctcggccc 300

cttaactacg gagggtatag tgagctagaa ttggattact ggggccaagg agtcatggtc 360

acagtctcct ca 372

<210> SEQ ID NO 51
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

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

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

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

Trp Leu Ala Thr Ile Cys Trp Glu Asp Ser Lys Gly Tyr Asn Pro Ser
50 55 60

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

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

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Cys Ala Arg Pro Leu Asn Tyr Gly Gly Tyr Ser Glu Leu Glu Leu Asp
100 105 110

Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 52
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Lys Ala Ser Gln Asn Ile Tyr Lys Tyr Leu Asn
1 5 10

<210> SEQ ID NO 53
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

Tyr Thr Asn Ser Leu Gln Thr
1 5

<210> SEQ ID NO 54
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Tyr Gln Tyr Asn Ser Gly Pro Thr
1 5

<210> SEQ ID NO 55
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

Thr Ser Gly Ile Cys Val Ser
1 5

<210> SEQ ID NO 56
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Thr Ile Cys Trp Glu Asp Ser Lys Gly Tyr Asn Pro Ser Leu Lys Asn
1 5 10 15

<210> SEQ ID NO 57
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

Pro Leu Asn Tyr Gly Gly Tyr Ser Glu Leu Glu Leu Asp Tyr
1 5 10

<210> SEQ ID NO 58
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

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uguaaaugcu guaacaauu 19

<210> SEQ ID NO 59
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

gcuguaaaug cuguaacaa 19

<210> SEQ ID NO 60
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

gugugguauc uguugcaaa 19

<210> SEQ ID NO 61
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

gcagacauug cgauaccaa 19

<210> SEQ ID NO 62
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

auaccaaugc agaagagaa 19

<210> SEQ ID NO 63
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

cuacagagcu gcagccuuu 19

<210> SEQ ID NO 64
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

gaagagagac accaacuuc 19

<210> SEQ ID NO 65
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

acuuccccau cugcaucuu 19

<210> SEQ ID NO 66
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 66

cugagcagca ccaccuauc 19

<210> SEQ ID NO 67
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

acagaugaga cagacuaca 19

<210> SEQ ID NO 68
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

caaugcagaa gagaaggaa 19

<210> SEQ ID NO 69
<211> LENGTH: 19
<212> TYPE: RNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

aauucccagu gugguaucu 19

<210> SEQ ID NO 70

<400> SEQUENCE: 70

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<210> SEQ ID NO 71

<400> SEQUENCE: 71

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<210> SEQ ID NO 72
<211> LENGTH: 193
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Met Gly Val His Glu Cys Pro Ala Trp Leu Trp Leu Leu Leu Ser Leu
1 5 10 15

Leu Ser Leu Pro Leu Gly Leu Pro Val Leu Gly Ala Pro Pro Arg Leu
20 25 30

Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
35 40 45

Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
50 55 60

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
65 70 75 80

Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
85 90 95

Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
100 105 110

Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
115 120 125

```
Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
    130                 135                 140

Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
145                 150                 155                 160

Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
                165                 170                 175

Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
            180                 185                 190

Arg
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<210> SEQ ID NO 73
<211> LENGTH: 193
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

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Met Gly Val His Glu Cys Pro Ala Trp Leu Trp Leu Leu Leu Ser Leu
1               5                   10                  15

Leu Ser Leu Pro Leu Gly Leu Pro Val Leu Gly Ala Pro Pro Arg Leu
            20                  25                  30

Ile Cys Asp Ser Arg Val Leu Glu Arg Tyr Leu Leu Glu Ala Lys Glu
        35                  40                  45

Ala Glu Asn Ile Thr Thr Gly Cys Ala Glu His Cys Ser Leu Asn Glu
    50                  55                  60

Asn Ile Thr Val Pro Asp Thr Lys Val Asn Phe Tyr Ala Trp Lys Arg
65                  70                  75                  80

Met Glu Val Gly Gln Gln Ala Val Glu Val Trp Gln Gly Leu Ala Leu
                85                  90                  95

Leu Ser Glu Ala Val Leu Arg Gly Gln Ala Leu Leu Val Asn Ser Ser
            100                 105                 110

Gln Pro Trp Glu Pro Leu Gln Leu His Val Asp Lys Ala Val Ser Gly
        115                 120                 125

Leu Arg Ser Leu Thr Thr Leu Leu Arg Ala Leu Gly Ala Gln Lys Glu
    130                 135                 140

Ala Ile Ser Pro Pro Asp Ala Ala Ser Ala Ala Pro Leu Arg Thr Ile
145                 150                 155                 160

Thr Ala Asp Thr Phe Arg Lys Leu Phe Arg Val Tyr Ser Asn Phe Leu
                165                 170                 175

Arg Gly Lys Leu Lys Leu Tyr Thr Gly Glu Ala Cys Arg Thr Gly Asp
            180                 185                 190

Arg
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<210> SEQ ID NO 74
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 74

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Xaa Ala Ser Asn Leu Glu Ser
1               5
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<210> SEQ ID NO 75
<211> LENGTH: 6

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 75

Xaa Gln Ser Asn Glu Glu
1 5

<210> SEQ ID NO 76
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 76

Gln Gln Xaa Asn Glu Xaa
1 5

<210> SEQ ID NO 77
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (16)..(16)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 77

Trp Ile Asn Thr Xaa Ser Gly Val Pro Thr Tyr Ala Asp Asp Phe Xaa
1 5 10 15

Gly

<210> SEQ ID NO 78
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(2)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(7)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 78

Xaa Xaa Tyr Tyr Gly Xaa Xaa Ala Xaa Tyr
1 5 10

<210> SEQ ID NO 79
<211> LENGTH: 75
<212> TYPE: DNA

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<213> ORGANISM: Mus musculus

<400> SEQUENCE: 79

gacaccaact tccccatctg catcttctgc tgtaaatgct gtaacaattc ccagtgtggt 60

atctgttgca aaaca 75

<210> SEQ ID NO 80
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 80

Asp Thr Asn Phe Pro Ile Cys Ile Phe Cys Cys Lys Cys Cys Asn Asn
1 5 10 15

Ser Gln Cys Gly Ile Cys Cys Lys Thr
20 25

<210> SEQ ID NO 81
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 81

gacaccaact tccccatatg cctcttctgc tgtaaatgct gtaagaattc ctcctgtggt 60

ctctgttgca taaca 75

<210> SEQ ID NO 82
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 82

Asp Thr Asn Phe Pro Ile Cys Leu Phe Cys Cys Lys Cys Cys Lys Asn
1 5 10 15

Ser Ser Cys Gly Leu Cys Cys Ile Thr
20 25

<210> SEQ ID NO 83
<211> LENGTH: 78
<212> TYPE: DNA
<213> ORGANISM: Cercopithecus aethiops

<400> SEQUENCE: 83

gacacccact tccccatctg cattttctgc tgcggctgct gtcatcgatc aaagtgtggg 60

atgtgctgca ggacgtag 78

<210> SEQ ID NO 84
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Cercopithecus aethiops

<400> SEQUENCE: 84

Asp Thr His Phe Pro Ile Cys Ile Phe Cys Cys Gly Cys Cys His Arg
1 5 10 15

Ser Lys Cys Gly Met Cys Cys Arg Thr
20 25

<210> SEQ ID NO 85
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Oryctolagus cuniculus

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<400> SEQUENCE: 85

gacacccact tccccatctg catcttctgc tgcagctgct gtaggaattc aaaatgtggg 60

atctgctgca agacc 75

<210> SEQ ID NO 86
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Oryctolagus cuniculus

<400> SEQUENCE: 86

Asp Thr His Phe Pro Ile Cys Ile Phe Cys Cys Ser Cys Cys Arg Asn
1 5 10 15

Ser Lys Cys Gly Ile Cys Cys Lys Thr
20 25

<210> SEQ ID NO 87
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 87

gacacccact tccccatctg catattctgc tgtggctgct gtaaaacacc gaagtgtggg 60

ctctgctgca taaca 75

<210> SEQ ID NO 88
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 88

Asp Thr His Phe Pro Ile Cys Ile Phe Cys Cys Gly Cys Cys Lys Thr
1 5 10 15

Pro Lys Cys Gly Leu Cys Cys Ile Thr
20 25

<210> SEQ ID NO 89
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 89

gacacccact tccccatctg catattctgc tgtggctgct gtaaaacacc gaagtgtggg 60

ttctgctgca ggacg 75

<210> SEQ ID NO 90
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 90

Asp Thr His Phe Pro Ile Cys Ile Phe Cys Cys Gly Cys Cys Lys Thr
1 5 10 15

Pro Lys Cys Gly Phe Cys Cys Arg Thr
20 25

<210> SEQ ID NO 91
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Canis familiaris

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<400> SEQUENCE: 91

gacacccact tccccatctg catattctgc tgtggctgct gtaaaacacc gaagtgtggg 60

ttgtgctgca agacg 75

<210> SEQ ID NO 92
<211> LENGTH: 25
<212> TYPE: PRT
<213> ORGANISM: Canis familiaris

<400> SEQUENCE: 92

Asp Thr His Phe Pro Ile Cys Ile Phe Cys Cys Gly Cys Cys Lys Thr
1 5 10 15

Pro Lys Cys Gly Leu Cys Cys Lys Thr
20 25

<210> SEQ ID NO 93
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

tctgttttcc cacaacagac gggacaactt gcagagctgc aaccccagga cagagctgga 60

gccagggcca gctggatgcc catgttccag aggcgaagga ggcgagacac ccacttcccc 120

atctgcattt tctgctgcgg ctgctgtcat cgatcaaagt gtgggatgtg ctgcaagacg 180

<210> SEQ ID NO 94
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

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

Asp Arg Ala Gly Ala Arg Ala Ser Trp Met Pro Met Phe Gln Arg Arg
20 25 30

Arg Arg Arg Asp Thr His Phe Pro Ile Cys Ile Phe Cys Cys Gly Cys
35 40 45

Cys His Arg Ser Lys Cys Gly Met Cys Cys Lys Thr
50 55 60

<210> SEQ ID NO 95
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

atctgcattt tctgctgcgg ctgctgtcat cgatcaaagt gtgggatgtg ctgcaagacg 60

<210> SEQ ID NO 96
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Ile Cys Ile Phe Cys Cys Gly Cys Cys His Arg Ser Lys Cys Gly Met
1 5 10 15

Cys Cys Lys Thr
20

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<210> SEQ ID NO 97
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

ttccccatct gcattttctg ctgcggctgc tgtcatcgat caaagtgtgg gatgtgctgc 60

aagacg 66

<210> SEQ ID NO 98
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Phe Pro Ile Cys Ile Phe Cys Cys Gly Cys Cys His Arg Ser Lys Cys
1 5 10 15

Gly Met Cys Cys Lys Thr
20

<210> SEQ ID NO 99
<211> LENGTH: 1650
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 99

agtccttaga ctgcacagca gaacagaagg catgatggca ctcagcactc ggacccaggc 60

tgcctgtctc ctgcttctcc tccttgccag cctgagcagc accacctatc tccatcaaca 120

ggtgagcacc ccaggcccat tgtggtggga gagccaggtc ccaggcaggc aggagctgct 180

caccactgag tagttagaat ggctcaggag tgatggcagc tgctgacaag gaagagggtg 240

gtccttagtg ggagctggga agctgcacag gtgtccttga atagctactc tgttgtccta 300

ctgtggaaaa tgaagcatgg tgggagccaa acaaaagtgt tccttggctg tcccaccccg 360

tcagggcatt ctttaagcag cctttacatg agtattttat aaagaattac tgtggatagt 420

acaaaagaca atgggcagaa aaactctaat gaggaaggac cagaggtggg gctaagaggc 480

tgacagccag gcaaagtatt ctatgagaaa atgatacaga agtcgggcag tggtggcaca 540

tgcctttaat cccagcattt gggaggcaga ggcaggtgga tttctgagtt tgaatccagc 600

ctggtctaca aagtgagttt caagacagcc agggctacac agagaaatcc tgtctgaaaa 660

aaaaaaaaaa acaaaaaaag aaaaaaaaaa tgatacagaa gggtctggag agatggctta 720

gctgttagga acatttgatg cttgtgcata ggacctagag tcagttccca gcacccatgt 780

ggtggatcac aaccatcctg aactctactt ccagggtacc tgatgccttc tgccctagat 840

ggcagtcagc agtaagcatg catatgatac acataggcac tcaaggcaat cacaagaccc 900

ttggggactg tagggtctga taagtgaagc cagtgttggc aataaagggc tgtagaggtt 960

ctgctgtgcc gagctttgtg gacagctgtg cagatgatga tctgtcctgg aaagccacaa 1020

tccagatgaa tgtgctataa gcctttgtgc tatggggtga cctggttata agagataaga 1080

tgcagggaaa actgtccgga gtgtgcaaaa gcaaagaaag tgggtgcttt taggagcatc 1140

caaggaatgg tgaggggaca cagggcagta ggagcccttc tagaaattct gtctaagcac 1200

agtccctaaa tctctgggga gaagctggca gagaaaagtc aggaagctat gccgggtact 1260

ccacaagatt caatacctct tctgctttca cagatgagac agactacaga gctgcagcct 1320

ttgcacgggg aagaaagcag ggcagacatt gcggtaagag catctgggac tccctccctg 1380

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atccccagcc tctcccatgc ccaagctagg ctgcttacct ctctttcttt acacagatac 1440

caatgcagaa gagaaggaag agagacacca acttccccat ctgcatcttc tgctgtaaat 1500

gctgtaacaa ttcccagtgt ggtatctgtt gcaaaacata gcctagagcc acatcctgac 1560

ctctctacac ccctgcagcc cctcaacccc attatttatt cctgccctcc ccaccaatga 1620

ccttgaaata aagacgattt tattttcaaa 1650

<210> SEQ ID NO 100
<211> LENGTH: 2637
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

gactgtcact cggtcccaga caccagagca agctcaagac ccagcagtgg gacagccaga 60

cagacggcac gatggcactg agctcccaga tctgggccgc ttgcctcctg ctcctcctcc 120

tcctcgccag cctgaccagt ggctctgttt tcccacaaca ggtgagagcc cagtggcctg 180

ggtccttagc agggcagcag ggatgggaga gccaggcctc agcctagggc actggagaca 240

cccgagcact gagcagagct caggacgtct caggagtact ggcagctgaa caggaaccag 300

gacaggcacg gtggctcatg cctgtaatcc cagcactttg ggaggttgag gcaggcagcc 360

cacttgaggt cagtttgaga ccagcctggc caacatggta aaaccccgtc tctactaaaa 420

atacaaaagt tagccaggct tggtggcagg tgcctgtaat cccagctact cgggagactg 480

aggcaggaga attgcttgaa cccgcaaggt ggaggttgca cagtgagctg agattgcacc 540

actgcactcc agcctggcaa cagagcaaga ctccatctcc aaaaaagaac agaaatcaat 600

gaagcaccga gtgacaggga ctggaaggtc ctaattccat gggtatttac ggaaccccta 660

cgccgtgtgg agtcttattc tagacagtgg ggacgaggcc atgaacaagg tagatgagag 720

aggagatttc tccatcctgg tcagggaatt tgttaaagac tgatgaaaac atgaataaat 780

aattgtgtct agtacattct attcgtgaat ctcataacag acagtggtag agtgaccgtg 840

acccattcgc cacacagtag agtcactttt ttggtttgtt ttttagagac agggtcttcc 900

tctgttgctg aggctggagt gcagtggtgc agtcatagtt cactgcagcc tcaacctcct 960

gtgctcaagc aatcctccca cctcagcgtc ccaagtagct gggacagcag gcacatgcca 1020

cgggttgggg gaccacaggc atggtcaagg ggctggcagt caagcaagtg tttcatgaga 1080

aagtgacagt tgaccttcgt cttggagggt gagagatgga ggcagcaaag acctaaggag 1140

aggacaagcc agcatagccc agggtcaggc tgaacaagag gagatggtgg gacttgggga 1200

taaggctgag gggtgggcag tccctaagtc ttgtgggcaa ccatgcagac actgattttt 1260

ccttggaata aagaggaagc ccccataagc ttttttttttt ttttctgaga tagggtctcg 1320

ctctgtcgtt caggctggtg tgcagtggca tcatctgggc tcactgcaac ctccgcctcc 1380

cgggttcaag caattctcct gcctcagctt cccgagcagc tgggattaca ggcggctgcc 1440

accacgcccg gctaattttt gtttttttag tagagacagg gtttcaccat gttggccaga 1500

ctggtcttga actcctgacc tcaggtgatt ctcccacctc ggcttcccaa agtgctggga 1560

ttacaggcgt gagccactgc gcccagcctc ctgtaggttt ttaaaatgga gaaaaccaca 1620

atctcactgg ccatgtttta aaaaacttaa tctgccagtc aggcaccatg gctcacacct 1680

gtaatcccag agttttggga ggccaaggta ggaagatcag ttgagcccag gagttcaaga 1740

ccagcttggg caacacaacc agaccccacc tctacaaaaa attaaaaaat tagccgggtg 1800

tggtggcgtg cacctgctgt cccagctact cgggaagctg aggcgggagc atcgcttgag 1860

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cacaggaggt caaggctgca gggagctatg actgtgccac tgcactctgg cctgggcaac 1920

agaggaagac tctgtctaaa aaacaaacaa aaaaagtgac tctgctgtgt ggcaaatgga 1980

ttgaggggca agaatgcagg gaggtgtgtt aggaggctgg cactggcatc caggcagggg 2040

aaggtgatat cccaaagaag agtagcagct gtggaaagag gaggaggcgg atctgggagg 2100

ttttttttttt taggaaaagc cgcccatggg aaggtgagca gaagcaagaa agcaaggccc 2160

ctcctaagag tccatttgag ctctgggttt aaaccacttg gagaggagca ggttgccggg 2220

agccagtctc agaggtccac tgggcccccc gccatcctct gcacccccctt ctgctttcac 2280

agacgggaca acttgcagag ctgcaacccc aggacagagc tggagccagg gccagctgga 2340

tggtgagcgc aacagtgatg cctttcctag ccccctgctc cctccccatg ctaaggccgg 2400

ttccctgctc acattccctt ccttcccaca gcccatgttc cagaggcgaa ggaggcgaga 2460

cacccacttc cccatctgca ttttctgctg cggctgctgt catcgatcaa agtgtgggat 2520

gtgctgcaag acgtagaacc tacctgccct gcccccgtcc cctcccttcc ttatttattc 2580

ctgctgcccc agaacatagg tcttggaata aaatggctgg ttcttttgtt ttccaaa 2637

<210> SEQ ID NO 101
<211> LENGTH: 180
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

tctgttttcc cacaacagac gggacaactt gcagagctgc aaccccagga cagagctgga 60

gccagggcca gctggatgcc catgttccag aggcgaagga ggcgagacac ccacttcccc 120

atctgcattt tctgctgcgg ctgctgtcat cgatcaaagt gtgggatgtg ctgcaagacg 180

<210> SEQ ID NO 102
<211> LENGTH: 61
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

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

Gln Asp Arg Ala Gly Ala Arg Ala Ser Trp Met Pro Met Phe Gln Arg
20 25 30

Arg Arg Arg Arg Asp Thr His Phe Pro Ile Cys Ile Phe Cys Cys Gly
35 40 45

Cys Cys His Arg Ser Lys Cys Gly Met Cys Cys Lys Thr
50 55 60

<210> SEQ ID NO 103
<211> LENGTH: 301
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

tcggccccgc ctcctgccac cgcagattgg ccgctagccc tccccgagcg ccctgcctcc 60

gagggccggc gcaccataaa agaagccgcc ctagccacgt cccctcgcag ttcggcggtc 120

ccgcgggtct gtctcttgct tcaacagtgt ttggacggaa cagatccggg gactctcttc 180

cagcctccga ccgccctccg atttcctctc cgcttgcaac ctccgggacc atcttctcgg 240

ccatctcctg cttctgggac ctgccagcac cgtttttgtg gttagctcct tcttgccaac 300

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c 301

<210> SEQ ID NO 104
<211> LENGTH: 75
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

gacacccact tccccatctg cattttctgc tgcggctgct gtcatcgatc aaagtgtggg 60

atgtgctgca agacg 75

<210> SEQ ID NO 105
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

ggggacaagt ttgtacaaaa aagcaggctt agatctgaat tcaatttacg cgtgggatcc 60

aaggtc 66

<210> SEQ ID NO 106

<400> SEQUENCE: 106

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<210> SEQ ID NO 107
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

gatattgtga tgacccagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctcctg catagtgatg gatacaacta tttggattgg 120

tacctgcaga agtcagggca gtctccacag cgcctgatct atatgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactccg 300

ctcactatcg gcggagggac caaggtggag atcaaa 336

<210> SEQ ID NO 108
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asp Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Ser Gly Gln Ser
35 40 45

Pro Gln Arg Leu Ile Tyr Met Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

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

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Leu Gln Thr Pro Leu Thr Ile Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 109
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agttatggca tgcactgggt ccgtcaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atttcatatg atggaagtaa tgaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgtat attactgtgt gagagatgtg 300

tggttcgggg agtccctcca cggtttggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 110
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Val Arg Asp Val Trp Phe Gly Glu Ser Leu His Gly Leu Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 111
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Arg Ser Ser Gln Ser Leu Leu His Ser Asp Gly Tyr Asn Tyr Leu Asp
1 5 10 15

<210> SEQ ID NO 112
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

Met Gly Ser Asn Arg Ala Ser
1 5

<210> SEQ ID NO 113
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Met Gln Ala Leu Gln Thr Pro Leu Thr
1 5

<210> SEQ ID NO 114
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 115
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 116
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

Asp Val Trp Phe Gly Glu Ser Leu His Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 117
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

cagtctgtgt tgacgcagcc gccctcactg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggggcagctc caacatcggg tcaggttttg ctatatactg gtaccagcag 120

cttccaggaa cagcccccaa actcctcatc tttggtgaca acattcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctccgcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttcg 300

gttttcggcg gagggaccaa gctgaccgtc cta 333

<210> SEQ ID NO 118
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

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

Arg Val Thr Ile Ser Cys Thr Gly Gly Ser Ser Asn Ile Gly Ser Gly
20 25 30

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

Leu Ile Phe Gly Asp Asn Ile Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95

Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> SEQ ID NO 119
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc     60

tcctgcaagg cttctggtta cacctttacc agctatggta tcagctgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtga aaaaaacact    180

gcacagaaac tccagggcag agtcaccatg accacagaca catccacgag cacagcctac    240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggaa    300

ctaggggctt ttgatatctg gggccaaggg acaatggtca ccgtctcttc a             351


<210> SEQ ID NO 120
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

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

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

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

Gly Trp Ile Ser Ala Tyr Asn Gly Glu Lys Asn Thr Ala Gln Lys Leu
    50                  55                  60

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

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

Ala Arg Glu Glu Leu Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
            100                 105                 110

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 121
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

Thr Gly Gly Ser Ser Asn Ile Gly Ser Gly Phe Ala Ile Tyr
1               5                   10
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<210> SEQ ID NO 122
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Gly Asp Asn Ile Arg Pro Ser
1 5

<210> SEQ ID NO 123
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Val
1 5 10

<210> SEQ ID NO 124
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

Ser Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 125
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

Trp Ile Ser Ala Tyr Asn Gly Glu Lys Asn Thr Ala Gln Lys Leu Gln
1 5 10 15

Gly

<210> SEQ ID NO 126
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Glu Glu Leu Gly Ala Phe Asp Ile
1 5

<210> SEQ ID NO 127
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcaactact tagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcatcatcag cagactggag 240

cctgaagatt ttgtagtgta ttactgtcag cagtatggta gctcactcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 128

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<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

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

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

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ile Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Val Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 129
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

caggttcagc tggtgcagtc tggagatgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttatc aagtatggaa tcagttgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcggcgctt tcaatggtaa cacagactat 180

gcacggaacc tccaggccag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtat attactgtgc gagagagggc 300

tggaacgacg actacttctg cggtttggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 130
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

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

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

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

Gly Trp Ile Gly Ala Phe Asn Gly Asn Thr Asp Tyr Ala Arg Asn Leu
50 55 60

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

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

Ala Arg Glu Gly Trp Asn Asp Asp Tyr Phe Cys Gly Leu Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser

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115 120

<210> SEQ ID NO 131
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

Arg Ala Ser Gln Ser Val Ser Ser Asn Tyr Leu Ala
1 5 10

<210> SEQ ID NO 132
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> SEQ ID NO 133
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Gln Gln Tyr Gly Ser Ser Leu Thr
1 5

<210> SEQ ID NO 134
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Lys Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 135
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

Trp Ile Gly Ala Phe Asn Gly Asn Thr Asp Tyr Ala Arg Asn Leu Gln
1 5 10 15

Ala

<210> SEQ ID NO 136
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Glu Gly Trp Asn Asp Asp Tyr Phe Cys Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 137
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc cagcctcacc 60

tgctctggag ataaattggg ggatagatat gcttcctggt atcagcagaa gccaggccag 120

tcccctgtgc tggtcatcta tcaagatagc aagcggccct cagggatccc tgagcgattc 180

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat 240

gaggctgact attactgtca ggcgtgggac agcagcactg catgtgtctt cggaactggg 300

accaaggtca ccgtccta 318

<210> SEQ ID NO 138
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

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

Ala Ser Leu Thr Cys Ser Gly Asp Lys Leu Gly Asp Arg Tyr Ala Ser
20 25 30

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

Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn
50 55 60

Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp
65 70 75 80

Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala Cys Val
85 90 95

Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> SEQ ID NO 139
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccctcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atgaaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgttgaat 240

ctgcaaatga acagcctgag agccgaggac acggctttgt attactgtgc gagagccggt 300

atagcagcag cccttgatgc ttttgatatc tggggccaag ggacaatggt caccgtctct 360

tca 363

<210> SEQ ID NO 140
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

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Ala Val Ile Trp Tyr Asp Glu Ser Asn Lys Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Asn
65                  70                  75                  80

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

Ala Arg Ala Gly Ile Ala Ala Ala Leu Asp Ala Phe Asp Ile Trp Gly
            100                 105                 110

Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 141
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

Ser Gly Asp Lys Leu Gly Asp Arg Tyr Ala Ser
1               5                   10


<210> SEQ ID NO 142
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

Gln Asp Ser Lys Arg Pro Ser
1               5


<210> SEQ ID NO 143
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

Gln Ala Trp Asp Ser Ser Thr Ala Cys Val
1               5                   10


<210> SEQ ID NO 144
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

Ser Tyr Gly Met His
1               5


<210> SEQ ID NO 145
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

Val Ile Trp Tyr Asp Glu Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1               5                   10                  15

Gly


<210> SEQ ID NO 146
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146
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Ala Gly Ile Ala Ala Ala Leu Asp Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 147
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

cagtctgtgt tgacgcagcc gccctcactg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggggcagctc caacatcggg tcaggttttg ctatatactg gtaccagcag 120

cttccaggaa cagcccccaa actcctcatc tatggtgaca acattcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctggc acctccgcct ccctggccat cactgggctc 240

caggctgagg atgaggctga ttattactgc cagtcctatg acagcagcct gagtggttcg 300

gtattcggcg gagggaccaa gctgaccgtc cta 333

<210> SEQ ID NO 148
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

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

Arg Val Thr Ile Ser Cys Thr Gly Gly Ser Ser Asn Ile Gly Ser Gly
20 25 30

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

Leu Ile Tyr Gly Asp Asn Ile Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 149
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agctatggta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtga aacaaacact 180

gcacagaaac tccagggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggaa 300

ctaggggctt ttgatatctg gggccaaggg acaatggtca ccgtctcttc a 351

<210> SEQ ID NO 150
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

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

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

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

Gly Trp Ile Ser Ala Tyr Asn Gly Glu Thr Asn Thr Ala Gln Lys Leu
50 55 60

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

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

Ala Arg Glu Glu Leu Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 151
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

Thr Gly Gly Ser Ser Asn Ile Gly Ser Gly Phe Ala Ile Tyr
1 5 10

<210> SEQ ID NO 152
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

Gly Asp Asn Ile Arg Pro Ser
1 5

<210> SEQ ID NO 153
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Val
1 5 10

<210> SEQ ID NO 154
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

Ser Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 155
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

Trp Ile Ser Ala Tyr Asn Gly Glu Thr Asn Thr Ala Gln Lys Leu Gln

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1 5 10 15

Gly

<210> SEQ ID NO 156
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

Glu Glu Leu Gly Ala Phe Asp Ile
1 5

<210> SEQ ID NO 157
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

tcctatgagc tgactcagcc accctcagtg tccgtgtccc caggacagac agccaccatc 60

acctgctctg gagataaatt gggggaaaga tatgcgtgtt ggtatcagca gaggccaggc 120

cagtcccctg tactggtcat ctatcaagat atcaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg 240

gatgaggctg actatttctg tcaggcgtgg tacagcagca ccaatgtgct tttcggcgga 300

gggaccaagc tgaccgtcct a 321

<210> SEQ ID NO 158
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

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

Thr Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu Gly Glu Arg Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ile Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr Ser Ser Thr Asn Val
85 90 95

Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 159
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg ctgaaagtaa taaatactac 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

-continued

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagcccag 300

gagggtatag cccctgacgc ttttgatatc tggggccaag gaacaatggt caccgtctct 360

tca 363

<210> SEQ ID NO 160
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 160

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

Ala Val Ile Trp Tyr Ala Glu Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Ala Gln Glu Gly Ile Ala Pro Asp Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 161
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

Ser Gly Asp Lys Leu Gly Glu Arg Tyr Ala Cys
1 5 10

<210> SEQ ID NO 162
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

Gln Asp Ile Lys Arg Pro Ser
1 5

<210> SEQ ID NO 163
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

Gln Ala Trp Tyr Ser Ser Thr Asn Val Leu
1 5 10

<210> SEQ ID NO 164
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 165
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

Val Ile Trp Tyr Ala Glu Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 166
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

Ala Gln Glu Gly Ile Ala Pro Asp Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 167
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

tcctatgagc tgactcagcc accctcagtg tccgtgtccc caggacagac agccaccatc 60

acctgctctg gagataaatt gggggaaaga tatgcgtgtt ggtatcagca gaggccaggc 120

cagtcccctg tactggtcat ctatcaagat agcaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg 240

gatgaggctg actatttctg tcaggcgtgg tacagcagca ccaatgtgct tttcggcgga 300

gggaccaagc tgaccgtcct a 321

<210> SEQ ID NO 168
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 168

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

Thr Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu Gly Glu Arg Tyr Ala
20 25 30

Cys Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro Val Leu Val Ile Tyr
35 40 45

Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr Ser Ser Thr Asn Val
85 90 95

Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 169

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<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 169

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg ctgaaagtaa taaatactac 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagcccag 300

gagggtatag cccctgacgc ttttgatatc tggggccaag gaacaatggt caccgtctct 360

tca 363

<210> SEQ ID NO 170
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 170

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

Ala Val Ile Trp Tyr Ala Glu Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Ala Gln Glu Gly Ile Ala Pro Asp Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 171
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 171

Ser Gly Asp Lys Leu Gly Glu Arg Tyr Ala Cys
1 5 10

<210> SEQ ID NO 172
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 172

Gln Asp Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 173
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 173

Gln Ala Trp Tyr Ser Ser Thr Asn Val Leu
1 5 10

<210> SEQ ID NO 174
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 174

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 175
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

Val Ile Trp Tyr Ala Glu Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 176
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Ala Gln Glu Gly Ile Ala Pro Asp Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 177
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

aattttatgc tgactcagcc ccactctgtg tcggagtctc cggggaagac ggtaaccatc 60

tcctgcaccc gcagcagtgg cagcattgcc agctactatg tgcagtggta ccagcagcgc 120

ccgggcagtt cccccaccac tgtgatctat gaggatagcc agagaccctc tggggtccct 180

gatcggttct ctggctccat cgacagctcc tccaactctg cctccctcac catctctgga 240

ctgaagactg aggacgaggc tgactattat tgtcagtctt atgatagcag caatgtggta 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 178
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly Lys
1 5 10 15

Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser Tyr
20 25 30

Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr Val
35 40 45

Ile Tyr Glu Asp Ser Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser

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    50                  55                  60

Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr Ile Ser Gly
65                  70                  75                  80

Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
                85                  90                  95

Ser Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> SEQ ID NO 179
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

caggtacagc tgcagcagtc aggtccagga ctggtgaagc cctcgcagac cctctcactc     60

acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg    120

cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggttt    180

aatgattatg cagtatctgt gcaaagtcga ataaccatca acccagacac atccaagaac    240

cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca    300

agagggattg tcttctccta cgctatggac gtctggggcc aagggaccac ggtcaccgtc    360

tcctca                                                               366


<210> SEQ ID NO 180
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

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

Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser Val Ser Ser Asn
            20                  25                  30

Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser Arg Gly Leu Glu
        35                  40                  45

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Phe Asn Asp Tyr Ala
    50                  55                  60

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

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

Tyr Tyr Cys Ala Arg Gly Ile Val Phe Ser Tyr Ala Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 181
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Thr Arg Ser Ser Gly Ser Ile Ala Ser Tyr Tyr Val Gln
1               5                   10


<210> SEQ ID NO 182
<211> LENGTH: 7
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-continued

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

Glu Asp Ser Gln Arg Pro Ser
1 5

<210> SEQ ID NO 183
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Gln Ser Tyr Asp Ser Ser Asn Val Val
1 5

<210> SEQ ID NO 184
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

Ser Asn Ser Ala Ala Trp Asn
1 5

<210> SEQ ID NO 185
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Arg Thr Tyr Tyr Arg Ser Lys Trp Phe Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Gln Ser

<210> SEQ ID NO 186
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

Gly Ile Val Phe Ser Tyr Ala Met Asp Val
1 5 10

<210> SEQ ID NO 187
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

tcctatgagc tgactcagcc cccctcagtg tccgtgtccc caggacagac agccagcatc 60

acctgttctg gagataaaat gggggaaaga tatgcttgct ggtatcagca gaagccaggc 120

cagtccccta tactggtcat ctatcaagat accaagcggc cctcagggat ccctgagcga 180

ttctctggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctatg 240

gatgaggctg actattactg tcaggcgtgg tacagcagca ccaatgtggt attcggcgga 300

gggaccaagc tgaccgtcct a 321

<210> SEQ ID NO 188
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 188

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

Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Met Gly Glu Arg Tyr Ala
20 25 30

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

Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Tyr Ser Ser Thr Asn Val
85 90 95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105

<210> SEQ ID NO 189
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg ttggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagcccag 300

gagggtatgg cccctgatgc ttttgatatc tggggccaag ggacaatggt caccgtctct 360

tca 363

<210> SEQ ID NO 190
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

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

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

Ala Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

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

Ala Arg Ala Gln Glu Gly Met Ala Pro Asp Ala Phe Asp Ile Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser
115 120

-continued

<210> SEQ ID NO 191
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191

Ser Gly Asp Lys Met Gly Glu Arg Tyr Ala Cys
1 5 10

<210> SEQ ID NO 192
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192

Gln Asp Thr Lys Arg Pro Ser
1 5

<210> SEQ ID NO 193
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

Gln Ala Trp Tyr Ser Ser Thr Asn Val Val
1 5 10

<210> SEQ ID NO 194
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

Asn Tyr Gly Met His
1 5

<210> SEQ ID NO 195
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 196
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

Ala Gln Glu Gly Met Ala Pro Asp Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 197
<211> LENGTH: 717
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

atgaggctcc ctgctcagct cctggggctg ctaatgctct gggtctctgg atccagtggg 60

gatattgtga tgacccagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 120

-continued

atctcctgca ggtctagtca gagcctcctg catagtgatg gatacaacta tttggattgg 180

tacctgcaga agtcagggca gtctccacag cgcctgatct atatgggttc taatcgggcc 240

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 300

agcagagtgg aggctgagga tgttggggtt tattactgca tgcaagctct acaaactccg 360

ctcactatcg gcggagggac caaggtggag atcaaacgaa ctgtggctgc accatctgtc 420

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 480

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 540

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 600

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 660

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 717

<210> SEQ ID NO 198
<211> LENGTH: 239
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

Met Arg Leu Pro Ala Gln Leu Leu Gly Leu Leu Met Leu Trp Val Ser
1 5 10 15

Gly Ser Ser Gly Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro
20 25 30

Val Thr Pro Gly Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser
35 40 45

Leu Leu His Ser Asp Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys
50 55 60

Ser Gly Gln Ser Pro Gln Arg Leu Ile Tyr Met Gly Ser Asn Arg Ala
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr
100 105 110

Cys Met Gln Ala Leu Gln Thr Pro Leu Thr Ile Gly Gly Gly Thr Lys
115 120 125

Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
130 135 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145 150 155 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
165 170 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
180 185 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
195 200 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> SEQ ID NO 199
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 199

atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag 60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc 120

tgtgcagcct ctggattcac cttcagtagt tatggcatgc actgggtccg tcaggctcca 180

ggcaaggggc tggagtgggt ggcagttatt tcatatgatg gaagtaatga atactatgca 240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300

caaatgaaca gcctgagagc tgaggacacg gctgtatatt actgtgtgag agatgtgtgg 360

ttcggggagt ccctccacgg tttggacgtc tggggccaag ggaccacggt caccgtctcc 420

tcagcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 480

gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 540

tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 600

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 660

acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 720

cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 840

tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 900

ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 960

cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa a 1401

<210> SEQ ID NO 200
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Val Ile Ser Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

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Tyr Tyr Cys Val Arg Asp Val Trp Phe Gly Glu Ser Leu His Gly Leu
        115                 120                 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
145                 150                 155                 160

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205

Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
    210                 215                 220

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
225                 230                 235                 240

Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
            340                 345                 350

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
        355                 360                 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    370                 375                 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405                 410                 415

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        435                 440                 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450                 455                 460

Pro Gly Lys
465


<210> SEQ ID NO 201
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

caggttcagc tggtgcagtc tggagatgag gtgaagaagc ctggggcctc agtgaaggtc     60
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tcctgcaagg cttctggtta caccttt atc aagtatggaa tcagttgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcggcgctt tcaatggtaa cacagactat 180

gcacggaacc tccaggccag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtat attactgtgc gagagagggc 300

tggaacgacg actacttctc cggtttggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 202
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

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

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

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

Gly Trp Ile Gly Ala Phe Asn Gly Asn Thr Asp Tyr Ala Arg Asn Leu
50 55 60

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

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

Ala Arg Glu Gly Trp Asn Asp Asp Tyr Phe Ser Gly Leu Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 203
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

Lys Tyr Gly Ile Ser
1 5

<210> SEQ ID NO 204
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

Trp Ile Gly Ala Phe Asn Gly Asn Thr Asp Tyr Ala Arg Asn Leu Gln
1 5 10 15

Ala

<210> SEQ ID NO 205
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

Glu Gly Trp Asn Asp Asp Tyr Phe Ser Gly Leu Asp Val
1 5 10

-continued

<210> SEQ ID NO 206
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

atggactgga cctggagcat ccttttcttg gtggcagcag caacaggtgc ccactcccag 60

gttcagctgg tgcagtctgg agatgaggtg aagaagcctg gggcctcagt gaaggtctcc 120

tgcaaggctt ctggttacac ctttatcaag tatggaatca gttgggtgcg acaggccct 180

ggacaagggc ttgagtggat gggatggatc ggcgctttca atggtaacac agactatgca 240

cggaacctcc aggccagagt caccatgacc acagacacat ccacgagcac agcctacatg 300

gagctgagga gcctgagatc tgacgacacg gccgtatatt actgtgcgag agagggctgg 360

aacgacgact acttctccgg tttggacgtc tggggccaag ggaccacggt caccgtctcc 420

tcagcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc 480

gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg 540

tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc 600

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag 660

acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag 720

cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc 780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg 840

tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac 900

ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc 960

cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag 1020

tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa 1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag 1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag 1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc 1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1380

ctctccctgt ctccgggtaa a 1401

<210> SEQ ID NO 207
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1 5 10 15

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Asp Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Ile Lys Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Met Gly Trp Ile Gly Ala Phe Asn Gly Asn Thr Asp Tyr Ala
65 70 75 80

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Arg Asn Leu Gln Ala Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Gly Trp Asn Asp Asp Tyr Phe Ser Gly Leu
        115                 120                 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
145                 150                 155                 160

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205

Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
    210                 215                 220

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
225                 230                 235                 240

Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
            340                 345                 350

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
        355                 360                 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    370                 375                 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405                 410                 415

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        435                 440                 445

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450                 455                 460

Pro Gly Lys
465


<210> SEQ ID NO 208
<211> LENGTH: 708
<212> TYPE: DNA
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

atggcctggt ctcctctcct cctcactctc ctcgctcact gcacagggtc ctgggcccag 60

tctgtgttga cgcagccgcc ctcactgtct ggggccccag ggcagagggt caccatctcc 120

tgcactgggg gcagctccaa catcgggtca ggttttgcta tatactggta ccagcagctt 180

ccaggaacag cccccaaact cctcatcttt ggtgacaaca ttcggccctc aggggtccct 240

gaccgattct ctggctccaa gtctggcacc tccgcctccc tggccatcac tgggctccag 300

gctgaggatg aggctgatta ttactgccag tcctatgaca gcagcctgag tggttcggtt 360

ttcggcggag ggaccaagct gaccgtccta agtcagccca aggctgcccc ctcggtcact 420

ctgttcccgc cctcctctga ggagcttcaa gccaacaagg ccacactggt gtgtctcata 480

agtgacttct acccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag 540

gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 600

tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 660

catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttca 708

<210> SEQ ID NO 209
<211> LENGTH: 236
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

Met Ala Trp Ser Pro Leu Leu Leu Thr Leu Leu Ala His Cys Thr Gly
1 5 10 15

Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Leu Ser Gly Ala
20 25 30

Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Gly Ser Ser Asn Ile
35 40 45

Gly Ser Gly Phe Ala Ile Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala
50 55 60

Pro Lys Leu Leu Ile Phe Gly Asp Asn Ile Arg Pro Ser Gly Val Pro
65 70 75 80

Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile
85 90 95

Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr
100 105 110

Asp Ser Ser Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr
115 120 125

Val Leu Ser Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro
130 135 140

Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile
145 150 155 160

Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser
165 170 175

Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser
180 185 190

Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln
195 200 205

Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser
210 215 220

Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser

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225 230 235

<210> SEQ ID NO 210
<211> LENGTH: 1386
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

atggactgga cctggagcat ccttttcttg gtggcagcag caacaggtgc ccactcccag 60

gttcagctgg tgcagtctgg agctgaggtg aagaagcctg gggcctcagt gaaggtctcc 120

tgcaaggctt ctggttacac ctttaccagc tatggtatca gctgggtgcg acaggcccct 180

ggacaagggc ttgagtggat gggatggatc agcgcttaca atggtgaaaa aaacactgca 240

cagaaactcc agggcagagt caccatgacc acagacacat ccacgagcac agcctacatg 300

gagctgagga gcctgagatc tgacgacacg gccgtgtatt actgtgcgag agaggaacta 360

ggggcttttg atatctgggg ccaagggaca atggtcaccg tctcttcagc ctccaccaag 420

ggcccatcgg tcttcccccc ggcgccctgc tccaggagca cctccgagag cacagcggcc 480

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 540

gctctgacca gcggcgtgca caccttccca gctgtcctac agtcctcagg actctactcc 600

ctcagcagcg tggtgaccgt gccctccagc aacttcggca cccagaccta cacctgcaac 660

gtagatcaca agcccagcaa caccaaggtg gacaagacag ttgagcgcaa atgttgtgtc 720

gagtgcccac cgtgcccagc accacctgtg gcaggaccgt cagtcttcct cttccccca 780

aaacccaagg acaccctcat gatctcccgg acccctgagg tcacgtgcgt ggtggtggac 840

gtgagccacg aagaccccga ggtccagttc aactggtacg tggacggcgt ggaggtgcat 900

aatgccaaga caaagccacg ggaggagcag ttcaacagca cgttccgtgt ggtcagcgtc 960

ctcaccgttg tgcaccagga ctggctgaac ggcaaggagt acaagtgcaa ggtctccaac 1020

aaaggcctcc cagccccat cgagaaaacc atctccaaaa ccaaagggca gccccgagaa 1080

ccacaggtgt acaccctgcc cccatcccgg gaggagatga ccaagaacca ggtcagcctg 1140

acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga gagcaatggg 1200

cagccggaga acaactacaa gaccacacct cccatgctgg actccgacgg ctccttcttc 1260

ctctacagca agctcaccgt ggacaagagc aggtggcagc aggggaacgt cttctcatgc 1320

tccgtgatgc atgaggctct gcacaaccac tacacgcaga agagcctctc cctgtctccg 1380

ggtaaa 1386

<210> SEQ ID NO 211
<211> LENGTH: 462
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211

Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1 5 10 15

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Ser Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Met Gly Trp Ile Ser Ala Tyr Asn Gly Glu Lys Asn Thr Ala

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```
65                  70                  75                  80

Gln Lys Leu Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Glu Leu Gly Ala Phe Asp Ile Trp Gly Gln
        115                 120                 125

Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
    130                 135                 140

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
145                 150                 155                 160

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

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
            180                 185                 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
        195                 200                 205

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
    210                 215                 220

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
225                 230                 235                 240

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
                245                 250                 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285

Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
305                 310                 315                 320

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
                405                 410                 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            420                 425                 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
        435                 440                 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210> SEQ ID NO 212
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
```

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<400> SEQUENCE: 212

tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc cagcctcacc 60

tgctctggag ataaattggg ggatagatat gcttcctggt atcagcagaa gccaggccag 120

tcccctgtgc tggtcatcta tcaagatagc aagcggccct cagggatccc tgagcgattc 180

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat 240

gaggctgact attactgtca ggcgtgggac agcagcactg catctgtctt cggaactggg 300

accaaggtca ccgtccta 318

<210> SEQ ID NO 213
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213

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

Ala Ser Leu Thr Cys Ser Gly Asp Lys Leu Gly Asp Arg Tyr Ala Ser
20 25 30

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

Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn
50 55 60

Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp
65 70 75 80

Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala Ser Val
85 90 95

Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105

<210> SEQ ID NO 214
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214

Ser Gly Asp Lys Leu Gly Asp Arg Tyr Ala Ser
1 5 10

<210> SEQ ID NO 215
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215

Gln Asp Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 216
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216

Gln Ala Trp Asp Ser Ser Thr Ala Ser Val
1 5 10

<210> SEQ ID NO 217

-continued

<211> LENGTH: 702
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217

atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcc 60

agatgttatg agctgactca gccaccctca gtgtccgtgt ccccaggaca gacagccagc 120

ctcacctgct ctggagataa attgggggat agatatgctt cctggtatca gcagaagcca 180

ggccagtccc ctgtgctggt catctatcaa gatagcaagc ggccctcagg gatccctgag 240

cgattctctg gctccaactc tgggaacaca gccactctga ccatcagcgg gacccaggct 300

atggatgagg ctgactatta ctgtcaggcg tgggacagca gcactgcatc tgtcttcgga 360

actgggacca aggtcaccgt cctaggtcag cccaaggcca accccactgt cactctgttc 420

ccgccctcct ctgaggagct ccaagccaac aaggccacac tagtgtgtct gatcagtgac 480

ttctacccgg gagctgtgac agtggcctgg aaggcagatg gcagccccgt caaggcggga 540

gtggagacca ccaaaccctc caaacagagc aacaacaagt acgcggccag cagctacctg 600

agcctgacgc ccgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 660

gggagcaccg tggagaagac agtggccct acagaatgtt ca 702

<210> SEQ ID NO 218
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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

Val Ser Pro Gly Gln Thr Ala Ser Leu Thr Cys Ser Gly Asp Lys Leu
35 40 45

Gly Asp Arg Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro
50 55 60

Val Leu Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu
65 70 75 80

Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser
85 90 95

Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp
100 105 110

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

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
145 150 155 160

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
165 170 175

Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
180 185 190

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
195 200 205

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
210 215 220

-continued

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225 230

<210> SEQ ID NO 219
<211> LENGTH: 702
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

atggaaaccc cagcgcagct tctcttcctc ctgctactct ggctcccaga taccaccgga 60

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 120

ctctcctgca gggccagtca gagtgttagc agcaactact tagcctggta ccagcagaaa 180

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 240

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcatcatcag cagactggag 300

cctgaagatt ttgtagtgta ttactgtcag cagtatggta gctcactcac tttcggcgga 360

gggaccaagg tggagatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcca 420

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat 480

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 540

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg 600

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 660

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt 702

<210> SEQ ID NO 220
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

Met Glu Thr Pro Ala Gln Leu Leu Phe Leu Leu Leu Leu Trp Leu Pro
1 5 10 15

Asp Thr Thr Gly Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser
20 25 30

Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser
35 40 45

Val Ser Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala
50 55 60

Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro
65 70 75 80

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Ile Ile
85 90 95

Ser Arg Leu Glu Pro Glu Asp Phe Val Val Tyr Tyr Cys Gln Gln Tyr
100 105 110

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

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
130 135 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145 150 155 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
165 170 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
180 185 190

-continued

```
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
        195                 200                 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
    210                 215                 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230


<210> SEQ ID NO 221
<211> LENGTH: 1401
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221

atggactgga cctggagcat ccttttcttg gtggcagcag caacaggtgc ccactcccag     60

gttcagctgg tgcagtctgg agatgaggtg aagaagcctg gggcctcagt gaaggtctcc    120

tgcaaggctt ctggttacac ctttatcaag tatggaatca gttgggtgcg acaggcccct    180

ggacaagggc ttgagtggat gggatggatc ggcgctttca atggtaacac agactatgca    240

cggaacctcc aggccagagt caccatgacc acagacacat ccacgagcac agcctacatg    300

gagctgagga gcctgagatc tgacgacacg gccgtatatt actgtgcgag agagggctgg    360

aacgacgact acttctgcgg tttggacgtc tggggccaag ggaccacggt caccgtctcc    420

tcagcctcca ccaagggccc atcggtcttc cccctggcgc cctgctccag gagcacctcc    480

gagagcacag cggccctggg ctgcctggtc aaggactact tccccgaacc ggtgacggtg    540

tcgtggaact caggcgctct gaccagcggc gtgcacacct tcccagctgt cctacagtcc    600

tcaggactct actccctcag cagcgtggtg accgtgccct ccagcaactt cggcacccag    660

acctacacct gcaacgtaga tcacaagccc agcaacacca aggtggacaa gacagttgag    720

cgcaaatgtt gtgtcgagtg cccaccgtgc ccagcaccac ctgtggcagg accgtcagtc    780

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcacg    840

tgcgtggtgg tggacgtgag ccacgaagac cccgaggtcc agttcaactg gtacgtggac    900

ggcgtggagg tgcataatgc caagacaaag ccacgggagg agcagttcaa cagcacgttc    960

cgtgtggtca gcgtcctcac cgttgtgcac caggactggc tgaacggcaa ggagtacaag   1020

tgcaaggtct ccaacaaagg cctcccagcc cccatcgaga aaaccatctc caaaaccaaa   1080

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggagga gatgaccaag   1140

aaccaggtca gcctgacctg cctggtcaaa ggcttctacc ccagcgacat cgccgtggag   1200

tgggagagca atgggcagcc ggagaacaac tacaagacca cacctcccat gctggactcc   1260

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   1320

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc   1380

ctctccctgt ctccgggtaa a                                             1401


<210> SEQ ID NO 222
<211> LENGTH: 467
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

Met Asp Trp Thr Trp Ser Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                   10                  15

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Asp Glu Val Lys Lys
            20                  25                  30
```

-continued

```
Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
        35                  40                  45

Ile Lys Tyr Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Trp Ile Gly Ala Phe Asn Gly Asn Thr Asp Tyr Ala
65                  70                  75                  80

Arg Asn Leu Gln Ala Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Gly Trp Asn Asp Asp Tyr Phe Cys Gly Leu
        115                 120                 125

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr
    130                 135                 140

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser
145                 150                 155                 160

Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
                165                 170                 175

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
            180                 185                 190

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
        195                 200                 205

Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys
    210                 215                 220

Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu
225                 230                 235                 240

Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala
                245                 250                 255

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
            260                 265                 270

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        275                 280                 285

Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    290                 295                 300

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe
305                 310                 315                 320

Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly
                325                 330                 335

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile
            340                 345                 350

Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val
        355                 360                 365

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
    370                 375                 380

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
385                 390                 395                 400

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
                405                 410                 415

Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            420                 425                 430

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        435                 440                 445
```

-continued

```
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    450                 455                 460

Pro Gly Lys
465
```

<210> SEQ ID NO 223
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 223

```
tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc caccatcacc     60

tgctctggag ataaattggg ggaaagatat gcgtcttggt atcagcagag gccaggccag    120

tcccctgtac tggtcatcta tcaagatatc aagcggccct cagggatccc tgagcgattc    180

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat    240

gaggctgact atttctgtca ggcgtggtac agcagcacca atgtgctttt cggcggaggg    300

accaagctga ccgtccta                                                  318
```

<210> SEQ ID NO 224
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

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

Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu Gly Glu Arg Tyr Ala Ser
            20                  25                  30

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

Asp Ile Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn
    50                  55                  60

Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp
65                  70                  75                  80

Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr Ser Ser Thr Asn Val Leu
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> SEQ ID NO 225
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

```
Ser Gly Asp Lys Leu Gly Glu Arg Tyr Ala Ser
1               5                   10
```

<210> SEQ ID NO 226
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

```
Gln Asp Ile Lys Arg Pro Ser
1               5
```

<210> SEQ ID NO 227

-continued

<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 227

Gln Ala Trp Tyr Ser Ser Thr Asn Val Leu
1 5 10

<210> SEQ ID NO 228
<211> LENGTH: 702
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcc 60

agatgttatg agctgactca gccaccctca gtgtccgtgt ccccaggaca gacagccacc 120

atcacctgct ctggagataa attgggggaa agatatgcgt cttggtatca gcagaggcca 180

ggccagtccc ctgtactggt catctatcaa gatatcaagc ggccctcagg gatccctgag 240

cgattctctg gctccaactc tgggaacaca gccactctga ccatcagcgg gacccaggct 300

atggatgagg ctgactattt ctgtcaggcg tggtacagca gcaccaatgt gcttttcggc 360

ggagggacca agctgaccgt cctaggtcag cccaaggctg ccccctcggt cactctgttc 420

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 480

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 540

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 600

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 660

gggagcaccg tggagaagac agtggccct acagaatgtt ca 702

<210> SEQ ID NO 229
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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

Val Ser Pro Gly Gln Thr Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu
35 40 45

Gly Glu Arg Tyr Ala Ser Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro
50 55 60

Val Leu Val Ile Tyr Gln Asp Ile Lys Arg Pro Ser Gly Ile Pro Glu
65 70 75 80

Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser
85 90 95

Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr
100 105 110

Ser Ser Thr Asn Val Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
115 120 125

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
145 150 155 160

-continued

```
Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
                165                 170                 175

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
            180                 185                 190

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
        195                 200                 205

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
    210                 215                 220

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230
```

<210> SEQ ID NO 230
<211> LENGTH: 696
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 230

```
atggcatgga tccctctctt cctcggcgtc cttgcttact gcacaggatc cgtggcctcc     60

tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc cagcctcacc    120

tgctctggag ataaattggg ggatagatat gcttcctggt atcagcagaa gccaggccag    180

tcccctgtgc tggtcatcta tcaagatagc aagcggccct cagggatccc tgagcgattc    240

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat    300

gaggctgact attactgtca ggcgtgggac agcagcactg catgtgtctt cggaactggg    360

accaaggtca ccgtcctagg tcagcccaag gccaacccca ctgtcactct gttcccgccc    420

tcctctgagg agctccaagc caacaaggcc acactagtgt gtctgatcag tgacttctac    480

ccgggagctg tgacagtggc ctggaaggca gatggcagcc ccgtcaaggc gggagtggag    540

accaccaaac cctccaaaca gagcaacaac aagtacgcgg ccagcagcta cctgagcctg    600

acgcccgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc    660

accgtggaga agacagtggc ccctacagaa tgttca                              696
```

<210> SEQ ID NO 231
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 231

```
Met Ala Trp Ile Pro Leu Phe Leu Gly Val Leu Ala Tyr Cys Thr Gly
1               5                   10                  15

Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
            20                  25                  30

Pro Gly Gln Thr Ala Ser Leu Thr Cys Ser Gly Asp Lys Leu Gly Asp
        35                  40                  45

Arg Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu
    50                  55                  60

Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                85                  90                  95

Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser
            100                 105                 110

Thr Ala Cys Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu Gly Gln
        115                 120                 125
```

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Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
                165                 170                 175

Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
        195                 200                 205

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
    210                 215                 220

Thr Val Ala Pro Thr Glu Cys Ser
225                 230


<210> SEQ ID NO 232
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag     60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc    120

tgtgcagcgt ctggattcac cctcagtagc tatggcatgc actgggtccg ccaggctcca    180

ggcaaggggc tggagtgggt ggcagttata tggtatgatg aaagtaataa atactatgca    240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gttgaatctg    300

caaatgaaca gcctgagagc cgaggacacg gctttgtatt actgtgcgag agccggtata    360

gcagcagccc ttgatgcttt tgatatctgg ggccaaggga caatggtcac cgtctcttca    420

gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag    480

agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg    540

tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca    600

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc    660

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc    720

aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc    780

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc    840

gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc    900

gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt    960

gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc   1020

aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg   1080

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac   1140

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg   1200

gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac   1260

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac   1320

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   1380

tccctgtctc cgggtaaa                                                 1398


<210> SEQ ID NO 233
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-continued

<211> LENGTH: 466
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Leu
35 40 45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Val Ile Trp Tyr Asp Glu Ser Asn Lys Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Asn Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu
100 105 110

Tyr Tyr Cys Ala Arg Ala Gly Ile Ala Ala Ala Leu Asp Ala Phe Asp
115 120 125

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
130 135 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145 150 155 160

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
165 170 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
180 185 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
195 200 205

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
210 215 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225 230 235 240

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
245 250 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
260 265 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
275 280 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
290 295 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305 310 315 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
325 330 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
340 345 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
355 360 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
370 375 380

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

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385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465


<210> SEQ ID NO 234
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc caccatcacc     60

tgctctggag ataaattggg ggaaagatat gcgtcttggt atcagcagag gccaggccag    120

tcccctgtac tggtcatcta tcaagatagc aagcggccct cagggatccc tgagcgattc    180

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat    240

gaggctgact atttctgtca ggcgtggtac agcagcacca atgtgctttt cggcggaggg    300

accaagctga ccgtccta                                                  318


<210> SEQ ID NO 235
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

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

Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu Gly Glu Arg Tyr Ala Ser
            20                  25                  30

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

Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn
    50                  55                  60

Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp
65                  70                  75                  80

Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr Ser Ser Thr Asn Val Leu
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210> SEQ ID NO 236
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

Ser Gly Asp Lys Leu Gly Glu Arg Tyr Ala Ser
1               5                   10


<210> SEQ ID NO 237
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-continued

<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

Gln Asp Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 238
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

Gln Ala Trp Tyr Ser Ser Thr Asn Val Leu
1 5 10

<210> SEQ ID NO 239
<211> LENGTH: 702
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 239

atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcc 60

agatgttatg agctgactca gccaccctca gtgtccgtgt ccccaggaca gacagccacc 120

atcacctgct ctggagataa attgggggaa agatatgcgt cttggtatca gcagaggcca 180

ggccagtccc ctgtactggt catctatcaa gatagcaagc ggccctcagg gatccctgag 240

cgattctctg gctccaactc tgggaacaca gccactctga ccatcagcgg gacccaggct 300

atggatgagg ctgactattt ctgtcaggcg tggtacagca gcaccaatgt gcttttcggc 360

ggagggacca agctgaccgt cctaggtcag cccaaggctg ccccctcggt cactctgttc 420

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 480

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 540

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 600

agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 660

gggagcaccg tggagaagac agtggccccct acagaatgtt ca 702

<210> SEQ ID NO 240
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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

Val Ser Pro Gly Gln Thr Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu
35 40 45

Gly Glu Arg Tyr Ala Ser Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro
50 55 60

Val Leu Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu
65 70 75 80

Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser
85 90 95

Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr

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            100                 105                 110

Ser Ser Thr Asn Val Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
        115                 120                 125

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
145                 150                 155                 160

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
                165                 170                 175

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
            180                 185                 190

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
        195                 200                 205

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
    210                 215                 220

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230


<210> SEQ ID NO 241
<211> LENGTH: 708
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

atggcctggt ctcctctcct cctcactctc ctcgctcact gcacagggtc ctgggcccag     60

tctgtgttga cgcagccgcc ctcactgtct ggggccccag ggcagagggt caccatctcc    120

tgcactgggg gcagctccaa catcgggtca ggttttgcta tatactggta ccagcagctt    180

ccaggaacag cccccaaact cctcatctat ggtgacaaca ttcggccctc aggggtccct    240

gaccgattct ctggctccaa gtctggcacc tccgcctccc tggccatcac tgggctccag    300

gctgaggatg aggctgatta ttactgccag tcctatgaca gcagcctgag tggttcggta    360

ttcggcggag ggaccaagct gaccgtccta agtcagccca aggctgcccc ctcggtcact    420

ctgttcccgc cctcctctga ggagcttcaa gccaacaagg ccacactggt gtgtctcata    480

agtgacttct acccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag    540

gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc    600

tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg    660

catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttca                 708


<210> SEQ ID NO 242
<211> LENGTH: 236
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242

Met Ala Trp Ser Pro Leu Leu Leu Thr Leu Leu Ala His Cys Thr Gly
1               5                   10                  15

Ser Trp Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Leu Ser Gly Ala
            20                  25                  30

Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Gly Ser Ser Asn Ile
        35                  40                  45

Gly Ser Gly Phe Ala Ile Tyr Trp Tyr Gln Gln Leu Pro Gly Thr Ala
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Gly Asp Asn Ile Arg Pro Ser Gly Val Pro
```

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65                  70                  75                  80

Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile
                85                  90                  95

Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr
            100                 105                 110

Asp Ser Ser Leu Ser Gly Ser Val Phe Gly Gly Gly Thr Lys Leu Thr
        115                 120                 125

Val Leu Ser Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro
    130                 135                 140

Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile
145                 150                 155                 160

Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser
                165                 170                 175

Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser
            180                 185                 190

Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln
        195                 200                 205

Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser
    210                 215                 220

Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230                 235


<210> SEQ ID NO 243
<211> LENGTH: 1329
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243

caggttcagc tggtgcagtc tggagctgag gtgaagaagc ctggggcctc agtgaaggtc     60

tcctgcaagg cttctggtta cacctttacc agctatggta tcagctgggt gcgacaggcc    120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtga aacaaacact    180

gcacagaaac tccagggcag agtcaccatg accacagaca catccacgag cacagcctac    240

atggagctga ggagcctgag atctgacgac acggccgtgt attactgtgc gagagaggaa    300

ctaggggctt ttgatatctg gggccaaggg acaatggtca ccgtctcttc agcctccacc    360

aagggcccat cggtcttccc cctggcgccc tgctccagga gcacctccga gagcacagcg    420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca    480

ggcgctctga ccagcggcgt gcacaccttc ccagctgtcc tacagtcctc aggactctac    540

tccctcagca gcgtggtgac cgtgccctcc agcaacttcg gcacccagac ctacacctgc    600

aacgtagatc acaagcccag caacaccaag gtggacaaga cagttgagcg caaatgttgt    660

gtcgagtgcc caccgtgccc agcaccacct gtggcaggac cgtcagtctt cctcttcccc    720

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacgtg cgtggtggtg    780

gacgtgagcc acgaagaccc cgaggtccag ttcaactggt acgtggacgg cgtggaggtg    840

cataatgcca agacaaagcc acgggaggag cagttcaaca gcacgttccg tgtggtcagc    900

gtcctcaccg ttgtgcacca ggactggctg aacggcaagg agtacaagtg caaggtctcc    960

aacaaaggcc tcccagcccc catcgagaaa accatctcca aaaccaaagg gcagccccga   1020

gaaccacagg tgtacaccct gcccccatcc cgggaggaga tgaccaagaa ccaggtcagc   1080

ctgacctgcc tggtcaaagg cttctacccc agcgacatcg ccgtggagtg ggagagcaat   1140

gggcagccgg agaacaacta caagaccaca cctcccatgc tggactccga cggctccttc   1200
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ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1260

tgctccgtga tgcatgaggc tctgcacaac cactacacgc agaagagcct ctccctgtct 1320

ccgggtaaa 1329

<210> SEQ ID NO 244
<211> LENGTH: 443
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

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

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

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

Gly Trp Ile Ser Ala Tyr Asn Gly Glu Thr Asn Thr Ala Gln Lys Leu
50 55 60

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

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

Ala Arg Glu Glu Leu Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

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

Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys
130 135 140

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

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

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

Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn
195 200 205

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

Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro
225 230 235 240

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

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn
260 265 270

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
275 280 285

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

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

Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys
325 330 335

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu

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            340                 345                 350

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        355                 360                 365

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    370                 375                 380

Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe
385                 390                 395                 400

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

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            420                 425                 430

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440


<210> SEQ ID NO 245
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

tatgagctga ctcagccccc ctcagtgtcc gtgtccccag gacagacagc cagcatcacc     60

tgttctggag ataaaatggg ggaaagatat gcttcctggt atcagcagaa gccaggccag    120

tcccctatac tggtcatcta tcaagatacc aagcggccct cagggatccc tgagcgattc    180

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat    240

gaggctgact attactgtca ggcgtggtac agcagcacca atgtggtatt cggcggaggg    300

accaagctga ccgtccta                                                  318


<210> SEQ ID NO 246
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246

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

Ala Ser Ile Thr Cys Ser Gly Asp Lys Met Gly Glu Arg Tyr Ala Ser
            20                  25                  30

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

Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser Asn
    50                  55                  60

Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met Asp
65                  70                  75                  80

Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Tyr Ser Ser Thr Asn Val Val
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105


<210> SEQ ID NO 247
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247

Ser Gly Asp Lys Met Gly Glu Arg Tyr Ala Ser
1               5                   10
```

<210> SEQ ID NO 248
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

Gln Asp Thr Lys Arg Pro Ser
1 5

<210> SEQ ID NO 249
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

Gln Ala Trp Tyr Ser Ser Thr Asn Val Val
1 5 10

<210> SEQ ID NO 250
<211> LENGTH: 702
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

atggacatga gggtgcccgc tcagctcctg gggctcctgc tgctgtggct gagaggtgcc 60

agatgttatg agctgactca gccccctca gtgtccgtgt ccccaggaca gacagccagc 120

atcacctgtt ctggagataa aatgggggaa agatatgctt cctggtatca gcagaagcca 180

ggccagtccc ctatactggt catctatcaa gataccaagc ggccctcagg gatccctgag 240

cgattctctg gctccaactc tgggaacaca gccactctga ccatcagcgg gacccaggct 300

atggatgagg ctgactatta ctgtcaggcg tggtacagca gcaccaatgt ggtattcggc 360

ggagggacca agctgaccgt cctaggtcag cccaaggctg ccccctcggt cactctgttc 420

ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct cataagtgac 480

ttctacccgg gagccgtgac agtggcctgg aaggcagata gcagccccgt caaggcggga 540

gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag cagctatctg 600

agcctgacgc ctgaacagtg gaagtcccac agaagctaca gctgccaggt cacgcatgaa 660

gggagcaccg tggagaagac agtggccct acagaatgtt ca 702

<210> SEQ ID NO 251
<211> LENGTH: 234
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

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

Val Ser Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Met
35 40 45

Gly Glu Arg Tyr Ala Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro
50 55 60

Ile Leu Val Ile Tyr Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu
65 70 75 80

Arg Phe Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser

-continued

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                85                  90                  95

Gly Thr Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Tyr
            100                 105                 110

Ser Ser Thr Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
        115                 120                 125

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
145                 150                 155                 160

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
                165                 170                 175

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
            180                 185                 190

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
        195                 200                 205

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
    210                 215                 220

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230


<210> SEQ ID NO 252
<211> LENGTH: 696
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

atggcatgga tccctctctt cctcggcgtc cttgcttact gcacaggatc cgtggcctcc     60

tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc caccatcacc    120

tgctctggag ataaattggg ggaaagatat gcgtgttggt atcagcagag gccaggccag    180

tcccctgtac tggtcatcta tcaagatatc aagcggccct cagggatccc tgagcgattc    240

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat    300

gaggctgact atttctgtca ggcgtggtac agcagcacca atgtgctttt cggcggaggg    360

accaagctga ccgtcctagg tcagcccaag gctgcccccc cggtcactct gttcccgccc    420

tcctctgagg agcttcaagc caacaaggcc acactggtgt gtctcataag tgacttctac    480

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag    540

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg    600

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc    660

accgtggaga agacagtggc ccctacagaa tgttca                              696


<210> SEQ ID NO 253
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

Met Ala Trp Ile Pro Leu Phe Leu Gly Val Leu Ala Tyr Cys Thr Gly
1               5                   10                  15

Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
            20                  25                  30

Pro Gly Gln Thr Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu Gly Glu
        35                  40                  45

Arg Tyr Ala Cys Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro Val Leu
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    50                  55                  60

Val Ile Tyr Gln Asp Ile Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                85                  90                  95

Gln Ala Met Asp Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr Ser Ser
            100                 105                 110

Thr Asn Val Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
        115                 120                 125

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
                165                 170                 175

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
        195                 200                 205

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
    210                 215                 220

Thr Val Ala Pro Thr Glu Cys Ser
225                 230


<210> SEQ ID NO 254
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 254

atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag     60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc    120

tgtgcagcgt ctggattcac cttcagtagc tatggcatgc actgggtccg ccaggctcca    180

ggcaaggggc tggagtgggt ggcagttata tggtatgctg aaagtaataa atactacgca    240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg    300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agcccaggag    360

ggtatagccc ctgacgcttt tgatatctgg ggccaaggaa caatggtcac cgtctcttca    420

gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag    480

agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg    540

tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca    600

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc    660

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc    720

aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc    780

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc    840

gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc    900

gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt    960

gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc   1020

aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg   1080
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cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac   1140

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg   1200

gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac   1260

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac   1320

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   1380

tccctgtctc cgggtaaa                                                 1398


<210> SEQ ID NO 255
<211> LENGTH: 466
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 255

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Trp Tyr Ala Glu Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Ala Gln Glu Gly Ile Ala Pro Asp Ala Phe Asp
        115                 120                 125

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145                 150                 155                 160

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320
```

-continued

```
Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465
```

<210> SEQ ID NO 256
<211> LENGTH: 696
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 256

```
atggcatgga tccctctctt cctcggcgtc cttgcttact gcacaggatc cgtggcctcc     60

tatgagctga ctcagccacc ctcagtgtcc gtgtccccag gacagacagc caccatcacc    120

tgctctggag ataaattggg ggaaagatat gcgtgttggt atcagcagag gccaggccag    180

tcccctgtac tggtcatcta tcaagatagc aagcggccct cagggatccc tgagcgattc    240

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat    300

gaggctgact atttctgtca ggcgtggtac agcagcacca atgtgctttt cggcggaggg    360

accaagctga ccgtcctagg tcagcccaag gctgcccccc cggtcactct gttcccgccc    420

tcctctgagg agcttcaagc caacaaggcc acactggtgt gtctcataag tgacttctac    480

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag    540

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg    600

acgcctgagc agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc    660

accgtggaga agacagtggc ccctacagaa tgttca                              696
```

<210> SEQ ID NO 257
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 257

```
Met Ala Trp Ile Pro Leu Phe Leu Gly Val Leu Ala Tyr Cys Thr Gly
1               5                   10                  15

Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
            20                  25                  30

Pro Gly Gln Thr Ala Thr Ile Thr Cys Ser Gly Asp Lys Leu Gly Glu
        35                  40                  45
```

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Arg Tyr Ala Cys Trp Tyr Gln Gln Arg Pro Gly Gln Ser Pro Val Leu
    50                  55                  60

Val Ile Tyr Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                85                  90                  95

Gln Ala Met Asp Glu Ala Asp Tyr Phe Cys Gln Ala Trp Tyr Ser Ser
            100                 105                 110

Thr Asn Val Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
        115                 120                 125

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
                165                 170                 175

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
        195                 200                 205

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
    210                 215                 220

Thr Val Ala Pro Thr Glu Cys Ser
225                 230


<210> SEQ ID NO 258
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 258

atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag     60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc    120

tgtgcagcgt ctggattcac cttcagtagc tatggcatgc actgggtccg ccaggctcca    180

ggcaaggggc tggagtgggt ggcagttata tggtatgctg aaagtaataa atactacgca    240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg    300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agcccaggag    360

ggtatagccc ctgacgcttt tgatatctgg ggccaaggaa caatggtcac cgtctcttca    420

gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag    480

agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg    540

tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca    600

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc    660

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc    720

aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc    780

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc    840

gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc    900

gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt    960

gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc   1020
```

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```
aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg   1080

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac   1140

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg   1200

gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac   1260

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac   1320

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   1380

tccctgtctc cgggtaaa                                                1398


<210> SEQ ID NO 259
<211> LENGTH: 466
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 259

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                   10                  15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
        35                  40                  45

Ser Ser Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Ile Trp Tyr Ala Glu Ser Asn Lys Tyr Tyr Ala
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Ala Gln Glu Gly Ile Ala Pro Asp Ala Phe Asp
        115                 120                 125

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
    130                 135                 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145                 150                 155                 160

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
                165                 170                 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
            180                 185                 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
        195                 200                 205

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
    210                 215                 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225                 230                 235                 240

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300
```

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```
Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465


<210> SEQ ID NO 260
<211> LENGTH: 705
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 260

atggcctggg ctccactact tctcaccctc ctcgctcact gcacaggttc ttgggccaat     60

tttatgctga ctcagcccca ctctgtgtcg gagtctccgg ggaagacggt aaccatctcc    120

tgcacccgca gcagtggcag cattgccagc tactatgtgc agtggtacca gcagcgcccg    180

ggcagttccc ccaccactgt gatctatgag gatagccaga gaccctctgg ggtccctgat    240

cggttctctg gctccatcga cagctcctcc aactctgcct ccctcaccat ctctggactg    300

aagactgagg acgaggctga ctattattgt cagtcttatg atagcagcaa tgtggtattc    360

ggcggaggga ccaagctgac cgtcctaggt cagcccaagg ctgccccctc ggtcactctg    420

ttcccgccct cctctgagga gcttcaagcc aacaaggcca cactggtgtg tctcataagt    480

gacttctacc cgggagccgt gacagtggcc tggaaggcag atagcagccc cgtcaaggcg    540

ggagtggaga ccaccacacc ctccaaacaa agcaacaaca agtacgcggc cagcagctat    600

ctgagcctga cgcctgagca gtggaagtcc cacagaagct acagctgcca ggtcacgcat    660

gaagggagca ccgtggagaa gacagtggcc cctacagaat gttca                    705


<210> SEQ ID NO 261
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

Met Ala Trp Ala Pro Leu Leu Leu Thr Leu Leu Ala His Cys Thr Gly
1               5                   10                  15

Ser Trp Ala Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser
            20                  25                  30
```

-continued

```
Pro Gly Lys Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile
        35                  40                  45

Ala Ser Tyr Tyr Val Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro
    50                  55                  60

Thr Thr Val Ile Tyr Glu Asp Ser Gln Arg Pro Ser Gly Val Pro Asp
65                  70                  75                  80

Arg Phe Ser Gly Ser Ile Asp Ser Ser Ser Asn Ser Ala Ser Leu Thr
                85                  90                  95

Ile Ser Gly Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser
            100                 105                 110

Tyr Asp Ser Ser Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val
        115                 120                 125

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

Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser
145                 150                 155                 160

Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser
                165                 170                 175

Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn
            180                 185                 190

Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp
        195                 200                 205

Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr
    210                 215                 220

Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
225                 230                 235


<210> SEQ ID NO 262
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262

atgtctgtct ccttcctcat cttcctgccc gtgctgggcc tcccatgggg tgtcctgtca     60

caggtacagc tgcagcagtc aggtccagga ctggtgaagc cctcgcagac cctctcactc    120

acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg    180

cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggttt    240

aatgattatg cagtatctgt gcaaagtcga ataaccatca acccagacac atccaagaac    300

cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca    360

agagggattg tcttctccta cgctatggac gtctggggcc aagggaccac ggtcaccgtc    420

tcctcagcct ccaccaaggg cccatcggtc ttcccctgg cgccctgctc caggagcacc    480

tccgagagca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg    540

gtgtcgtgga actcaggcgc tctgaccagc ggcgtgcaca ccttcccagc tgtcctacag    600

tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcaa cttcggcacc    660

cagacctaca cctgcaacgt agatcacaag cccagcaaca ccaaggtgga caagacagtt    720

gagcgcaaat gttgtgtcga gtgcccaccg tgcccagcac cacctgtggc aggaccgtca    780

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc    840

acgtgcgtgg tggtggacgt gagccacgaa gaccccgagg tccagttcaa ctggtacgtg    900

gacggcgtgg aggtgcataa tgccaagaca aagccacggg aggagcagtt caacagcacg    960
```

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```
ttccgtgtgg tcagcgtcct caccgttgtg caccaggact ggctgaacgg caaggagtac   1020

aagtgcaagg tctccaacaa aggcctccca gcccccatcg agaaaaccat ctccaaaacc   1080

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga ggagatgacc   1140

aagaaccagg tcagcctgac ctgcctggtc aaaggcttct accccagcga catcgccgtg   1200

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacacctcc catgctggac   1260

tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag   1320

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag   1380

agcctctccc tgtctccggg taaa                                          1404


<210> SEQ ID NO 263
<211> LENGTH: 468
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263

Met Ser Val Ser Phe Leu Ile Phe Leu Pro Val Leu Gly Leu Pro Trp
1               5                   10                  15

Gly Val Leu Ser Gln Val Gln Leu Gln Gln Ser Gly Pro Gly Leu Val
            20                  25                  30

Lys Pro Ser Gln Thr Leu Ser Leu Thr Cys Ala Ile Ser Gly Asp Ser
        35                  40                  45

Val Ser Ser Asn Ser Ala Ala Trp Asn Trp Ile Arg Gln Ser Pro Ser
    50                  55                  60

Arg Gly Leu Glu Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Phe
65                  70                  75                  80

Asn Asp Tyr Ala Val Ser Val Gln Ser Arg Ile Thr Ile Asn Pro Asp
                85                  90                  95

Thr Ser Lys Asn Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu
            100                 105                 110

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ile Val Phe Ser Tyr Ala
        115                 120                 125

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser
    130                 135                 140

Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr
145                 150                 155                 160

Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro
                165                 170                 175

Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val
            180                 185                 190

His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser
        195                 200                 205

Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
    210                 215                 220

Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val
225                 230                 235                 240

Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val
                245                 250                 255

Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu
```

-continued

```
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr
305                 310                 315                 320

Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415

Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly Lys
465
```

<210> SEQ ID NO 264
<211> LENGTH: 696
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 264

```
atggcatgga tccctctctt cctcggcgtc cttgcttact gcacaggatc cgtggcctcc     60

tatgagctga ctcagccccc ctcagtgtcc gtgtccccag gacagacagc cagcatcacc    120

tgttctggag ataaaatggg ggaaagatat gcttgctggt atcagcagaa gccaggccag    180

tcccctatac tggtcatcta tcaagatacc aagcggccct cagggatccc tgagcgattc    240

tctggctcca actctgggaa cacagccact ctgaccatca gcgggaccca ggctatggat    300

gaggctgact attactgtca ggcgtggtac agcagcacca atgtggtatt cggcggaggg    360

accaagctga ccgtcctagg tcagcccaag gctgcccccc cggtcactct gttcccgccc    420

tcctctgagg agcttcaagc caacaaggcc acactggtgt gtctcataag tgacttctac    480

ccgggagccg tgacagtggc ctggaaggca gatagcagcc ccgtcaaggc gggagtggag    540

accaccacac cctccaaaca aagcaacaac aagtacgcgg ccagcagcta tctgagcctg    600

acgcctgaac agtggaagtc ccacagaagc tacagctgcc aggtcacgca tgaagggagc    660

accgtggaga agacagtggc ccctacagaa tgttca                              696
```

<210> SEQ ID NO 265
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265

```
Met Ala Trp Ile Pro Leu Phe Leu Gly Val Leu Ala Tyr Cys Thr Gly
1               5                   10                  15

Ser Val Ala Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ser
```

-continued

```
            20                  25                  30

Pro Gly Gln Thr Ala Ser Ile Thr Cys Ser Gly Asp Lys Met Gly Glu
        35                  40                  45

Arg Tyr Ala Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Ile Leu
    50                  55                  60

Val Ile Tyr Gln Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe
65                  70                  75                  80

Ser Gly Ser Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr
                85                  90                  95

Gln Ala Met Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Tyr Ser Ser
            100                 105                 110

Thr Asn Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
        115                 120                 125

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
    130                 135                 140

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
145                 150                 155                 160

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
                165                 170                 175

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
            180                 185                 190

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
        195                 200                 205

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
    210                 215                 220

Thr Val Ala Pro Thr Glu Cys Ser
225                 230


<210> SEQ ID NO 266
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266

atggagtttg ggctgagctg ggttttcctc gttgctcttt taagaggtgt ccagtgtcag     60

gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc    120

tgtgcagcgt ctggattcac cttcagtaac tatggcatgc actgggtccg ccaggctcca    180

ggcaaggggc tggagtgggt ggcagttata tggtatgttg gaagtaataa atactatgca    240

gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg    300

caaatgaaca gcctgagagc cgaggacacg gctgtgtatt actgtgcgag agcccaggag    360

ggtatggccc ctgatgcttt tgatatctgg ggccaaggga caatggtcac cgtctcttca    420

gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag    480

agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg    540

tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca    600

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc    660

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc    720

aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc    780

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc    840

gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc    900
```

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gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt 960

gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc 1020

aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg 1080

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac 1140

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg 1200

gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac 1260

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1320

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1380

tccctgtctc cgggtaaa 1398

<210> SEQ ID NO 267
<211> LENGTH: 466
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val Gln Cys Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
20 25 30

Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Asn Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ala Val Ile Trp Tyr Val Gly Ser Asn Lys Tyr Tyr Ala
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Ala Gln Glu Gly Met Ala Pro Asp Ala Phe Asp
115 120 125

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
130 135 140

Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu
145 150 155 160

Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
165 170 175

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
180 185 190

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
195 200 205

Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn
210 215 220

Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg
225 230 235 240

Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly
245 250 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
260 265 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
275 280 285

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```
Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465


<210> SEQ ID NO 268
<211> LENGTH: 711
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 268

atggagacag acacactcct gctatgggtg ctgctgctct gggttccagg ttccacaggt     60

aacatcgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc    120

atatcctgca gagccagtga aagtgttgat agttatggca atagttttat gcactggtac    180

cagcagaaac caggacagcc acccaaactc ctcatctatc ttgcatccaa cctagaatct    240

ggggtccctg ccaggttcag tggcagtggg tctaggacag acttcaccct caccattgat    300

cctgtggagg ctgatgatgc tgcaacctat tactgtcagc aaaataatga ggatcggacg    360

ttcggtggag gcaccaagct ggaaatcaaa cgggctgatg ctgcaccaac tgtatccatc    420

ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac    480

aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat    540

ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc    600

accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact    660

cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg t              711


<210> SEQ ID NO 269
<211> LENGTH: 237
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 269

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                   10                  15
```

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```
Gly Ser Thr Gly Asn Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
            20                  25                  30

Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
        35                  40                  45

Val Asp Ser Tyr Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro
    50                  55                  60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Leu Ala Ser Asn Leu Glu Ser
65                  70                  75                  80

Gly Val Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
                85                  90                  95

Leu Thr Ile Asp Pro Val Glu Ala Asp Asp Ala Ala Thr Tyr Tyr Cys
            100                 105                 110

Gln Gln Asn Asn Glu Asp Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
    130                 135                 140

Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
145                 150                 155                 160

Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
                165                 170                 175

Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
            180                 185                 190

Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
        195                 200                 205

Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser
    210                 215                 220

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


<210> SEQ ID NO 270
<211> LENGTH: 1419
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 270

atgggttggc tgtggaactt gctattcctg atggcagctg cccaaagtgc ccaagcacag     60

atccagttgg tacagtctgg acctgagctg aagaagcctg gagagacagt caagatctcc    120

tgcaaggctt ctgggtatac cttcacaacc tatggaatga gctgggtgaa acaggctcca    180

ggaaagggtt taaagtggat gggctggata aacacctact ctggagtgcc aacatatgct    240

gatgacttca agggacggtt tgccttctct ttggaaacct ctgccagcac tgcctatttg    300

cagatcaaca acctcaaaaa tgaggacacg gctacatatt tctgtgcaag cttatggtac    360

tacggtaggg cctttgacta ctggggccaa ggcaccactc tcacagtctc ctcagccaaa    420

acaacagccc catcggtcta tccactggcc cctgtgtgtg gaggtacaac tggctcctcg    480

gtgactctag gatgcctggt caagggttat ttccctgagc cagtgacctt gacctggaac    540

tctggatccc tgtccagtgg tgtgcacacc ttcccagctc tcctgcagtc tggcctctac    600

accctcagca gctcagtgac tgtaacctcg aacacctggc ccagccagac catcacctgc    660

aatgtggccc acccggcaag cagcaccaaa gtggacaaga aaattgagcc cagagtgccc    720

ataacacaga acccctgtcc tccactcaaa gagtgtcccc catgcgcagc tccagacctc    780

ttgggtggac catccgtctt catcttccct ccaaagatca aggatgtact catgatctcc    840
```

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ctgagcccca tggtcacatg tgtggtggtg gatgtgagcg aggatgaccc agacgtccag 900

atcagctggt ttgtgaacaa cgtggaagta cacacagctc agacacaaac ccatagagag 960

gattacaaca gtactctccg ggtggtcagt gccctcccca tccagcacca ggactggatg 1020

agtggcaagg agttcaaatg caaggtcaac aacagagccc tcccatcccc catcgagaaa 1080

accatctcaa aacccagagg gccagtaaga gctccacagg tatatgtctt gcctccacca 1140

gcagaagaga tgactaagaa agagttcagt ctgacctgca tgatcacagg cttcttacct 1200

gccgaaattg ctgtggactg gaccagcaat gggcgtacag agcaaaacta caagaacacc 1260

gcaacagtcc tggactctga tggttcttac ttcatgtaca gcaagctcag agtacaaaag 1320

agcacttggg aaagaggaag tcttttcgcc tgctcagtgg tccacgaggg tctgcacaat 1380

caccttacga ctaagaccat ctcccggtct ctgggtaaa 1419

<210> SEQ ID NO 271
<211> LENGTH: 473
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 271

Met Gly Trp Leu Trp Asn Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
20 25 30

Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Thr Tyr Gly Met Ser Trp Val Lys Gln Ala Pro Gly Lys Gly Leu
50 55 60

Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Val Pro Thr Tyr Ala
65 70 75 80

Asp Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser
85 90 95

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr
100 105 110

Tyr Phe Cys Ala Ser Leu Trp Tyr Tyr Gly Arg Ala Phe Asp Tyr Trp
115 120 125

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

Ser Val Tyr Pro Leu Ala Pro Val Cys Gly Gly Thr Thr Gly Ser Ser
145 150 155 160

Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr
165 170 175

Leu Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro
180 185 190

Ala Leu Leu Gln Ser Gly Leu Tyr Thr Leu Ser Ser Ser Val Thr Val
195 200 205

Thr Ser Asn Thr Trp Pro Ser Gln Thr Ile Thr Cys Asn Val Ala His
210 215 220

Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Glu Pro Arg Val Pro
225 230 235 240

Ile Thr Gln Asn Pro Cys Pro Pro Leu Lys Glu Cys Pro Pro Cys Ala
245 250 255

Ala Pro Asp Leu Leu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Lys
260 265 270

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```
Ile Lys Asp Val Leu Met Ile Ser Leu Ser Pro Met Val Thr Cys Val
        275                 280                 285

Val Val Asp Val Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe
    290                 295                 300

Val Asn Asn Val Glu Val His Thr Ala Gln Thr Gln Thr His Arg Glu
305                 310                 315                 320

Asp Tyr Asn Ser Thr Leu Arg Val Val Ser Ala Leu Pro Ile Gln His
                325                 330                 335

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

Ala Leu Pro Ser Pro Ile Glu Lys Thr Ile Ser Lys Pro Arg Gly Pro
        355                 360                 365

Val Arg Ala Pro Gln Val Tyr Val Leu Pro Pro Pro Ala Glu Glu Met
    370                 375                 380

Thr Lys Lys Glu Phe Ser Leu Thr Cys Met Ile Thr Gly Phe Leu Pro
385                 390                 395                 400

Ala Glu Ile Ala Val Asp Trp Thr Ser Asn Gly Arg Thr Glu Gln Asn
                405                 410                 415

Tyr Lys Asn Thr Ala Thr Val Leu Asp Ser Asp Gly Ser Tyr Phe Met
            420                 425                 430

Tyr Ser Lys Leu Arg Val Gln Lys Ser Thr Trp Glu Arg Gly Ser Leu
        435                 440                 445

Phe Ala Cys Ser Val Val His Glu Gly Leu His Asn His Leu Thr Thr
    450                 455                 460

Lys Thr Ile Ser Arg Ser Leu Gly Lys
465                 470
```

<210> SEQ ID NO 272
<211> LENGTH: 711
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 272

```
atggagacag acacactcct gctatgggtg ctgctgctct gggttccagg ttccacaggt     60

gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc    120

atatcctgca gagccagtga aagtgttgat agttatggca atagttttat gcactggtac    180

cagcagaaac caggacagcc acccaaactc ctcatctatc gtgcatccaa cctagaatct    240

gggatccctg ccaggttcag tggcagtggg tctaggacag acttcaccct caccattaat    300

cctgtggagg ctgatgatgt tgcaacctat tactgtcacc aaagtaatga ggagtacacg    360

ttcggagggg ggaccaagct ggaaataaaa cgggctgatg ctgcaccaac tgtatccatc    420

ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac    480

aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat    540

ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc    600

accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact    660

cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg t              711
```

<210> SEQ ID NO 273
<211> LENGTH: 237
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 273

-continued

```
Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1               5                  10                  15

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
            20                  25                  30

Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
        35                  40                  45

Val Asp Ser Tyr Gly Asn Ser Phe Met His Trp Tyr Gln Gln Lys Pro
    50                  55                  60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser
65                  70                  75                  80

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
                85                  90                  95

Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Thr Tyr Tyr Cys
            100                 105                 110

His Gln Ser Asn Glu Glu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
    130                 135                 140

Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
145                 150                 155                 160

Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
                165                 170                 175

Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
            180                 185                 190

Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
        195                 200                 205

Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser
    210                 215                 220

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


<210> SEQ ID NO 274
<211> LENGTH: 1383
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 274

atgggttggc tgtggaactt gctattcctg atggcagctg cccaaagtgc ccaagcacag     60

atccagttgg tacagtctgg acctgagctg aagaagcctg gagagacagt caagatctcc    120

tgcaaggctt ctgggtatac cttcacaacc tatggaatga gctgggtgaa acaggctcca    180

ggaaagggtt taaagtggat gggctggata aatacctact ctggagtgcc aacatatgct    240

gatgacttca agggacggtt tgccttctct ttggaaacct ctgccagcac tgcctatttg    300

cagatcaaca acctcaaaaa tgaggacacg gctacatatt tctgtggaag agaccactac    360

tacggggagg ttgcttactg gggccaaggg actctggtca ctgtctctgc agccaaaacg    420

acacccccat ctgtctatcc actggccgct ggatctgctg cccaaactaa ctccatggtg    480

accctgggat gcctggtcaa gggctatttc cctgagccag tgacagtgac ctggaactct    540

ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacact    600

ctgagcagct cagtgactgt cccctccagc acctggccca gccagaccgt cacctgcaac    660

gttgcccacc cggccagcag caccaaggtg gacaagaaaa ttgtgcccag ggattgtggt    720

tgtaagcctt gcatatgtac agtcccagaa gtatcatctg tcttcatctt cccccaaag     780
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cccaaggatg tgctcaccat tactctgact cctaaggtca cgtgtgttgt ggtagacatc 840

agcaaggatg atcccgaggt ccagttcagc tggtttgtag atgatgtgga ggtgcacaca 900

gctcagacga aaccccggga ggagcagatc aacagcactt tccgttcagt cagtgaactt 960

cccatcatgc accaggactg gctcaatggc aaggagttca aatgcagggt caacagtgca 1020

gctttccctg cccccatcga gaaaaccatc tccaaaacca aaggcagacc gaaggctcca 1080

caggtgtaca ccattccacc tcccaaggag cagatggcca aggataaagt cagtctgacc 1140

tgcatgataa caaacttctt ccctgaagac attactgtgg agtggcagtg gaatgggcag 1200

ccagcggaga actacaagaa cactcagccc atcatggaca cagatggctc ttacttcgtc 1260

tacagcaagc tcaatgtgca gaagagcaac tgggaggcag gaaatacttt cacctgctct 1320

gtgttacatg agggcctgca caaccaccat actgagaaga gcctctccca ctctcctggt 1380

aaa 1383

<210> SEQ ID NO 275
<211> LENGTH: 461
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 275

Met Gly Trp Leu Trp Asn Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
20 25 30

Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Thr Tyr Gly Met Ser Trp Val Lys Gln Ala Pro Gly Lys Gly Leu
50 55 60

Lys Trp Met Gly Trp Ile Asn Thr Tyr Ser Gly Val Pro Thr Tyr Ala
65 70 75 80

Asp Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser
85 90 95

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr
100 105 110

Tyr Phe Cys Gly Arg Asp His Tyr Tyr Gly Glu Val Ala Tyr Trp Gly
115 120 125

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

Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
145 150 155 160

Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
195 200 205

Ser Ser Thr Trp Pro Ser Gln Thr Val Thr Cys Asn Val Ala His Pro
210 215 220

Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
225 230 235 240

Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
245 250 255

Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys

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            260                 265                 270

Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
        275                 280                 285

Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Lys
    290                 295                 300

Pro Arg Glu Glu Gln Ile Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
305                 310                 315                 320

Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
                325                 330                 335

Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            340                 345                 350

Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
        355                 360                 365

Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
    370                 375                 380

Asn Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
385                 390                 395                 400

Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
                405                 410                 415

Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
            420                 425                 430

Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
        435                 440                 445

His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
    450                 455                 460


<210> SEQ ID NO 276
<211> LENGTH: 711
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 276

atggagacag acacactcct gctatgggtg ctgctgctct gggttccagg ttccacaggt     60

gacattgtgc tgacccaatc tccagcttct ttggctgtgt ctctagggca gagggccacc    120

atatcctgca gagccagtga aagtgttgat agttttggca atagttttat gcactggtac    180

cagctgaaac caggacagcc acccaaactc ctcatctatc gtgcatccaa cctagaatct    240

gggatccctg ccaggttcag tggcagtggg tctaggacag acttcaccct caccattaat    300

cctgtggagg ctgatgatgt tgcaatttat tactgtcagc aaagtaatga ggagtacacg    360

ttcggagggg ggaccaagct ggaaataaaa cgggctgatg ctgcaccaac tgtatccatc    420

ttcccaccat ccagtgagca gttaacatct ggaggtgcct cagtcgtgtg cttcttgaac    480

aacttctacc ccaaagacat caatgtcaag tggaagattg atggcagtga acgacaaaat    540

ggcgtcctga acagttggac tgatcaggac agcaaagaca gcacctacag catgagcagc    600

accctcacgt tgaccaagga cgagtatgaa cgacataaca gctatacctg tgaggccact    660

cacaagacat caacttcacc cattgtcaag agcttcaaca ggaatgagtg t              711


<210> SEQ ID NO 277
<211> LENGTH: 237
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 277

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
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1               5                   10                  15

Gly Ser Thr Gly Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala
            20                  25                  30

Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser
        35                  40                  45

Val Asp Ser Phe Gly Asn Ser Phe Met His Trp Tyr Gln Leu Lys Pro
    50                  55                  60

Gly Gln Pro Pro Lys Leu Leu Ile Tyr Arg Ala Ser Asn Leu Glu Ser
65                  70                  75                  80

Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Arg Thr Asp Phe Thr
                85                  90                  95

Leu Thr Ile Asn Pro Val Glu Ala Asp Asp Val Ala Ile Tyr Tyr Cys
            100                 105                 110

Gln Gln Ser Asn Glu Glu Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu
        115                 120                 125

Ile Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser
    130                 135                 140

Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn
145                 150                 155                 160

Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser
                165                 170                 175

Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys
            180                 185                 190

Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu
        195                 200                 205

Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser
    210                 215                 220

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


<210> SEQ ID NO 278
<211> LENGTH: 1383
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 278

atgggttggc tgtggaactt gctattcctg atggcagctg cccaaagtgc ccaagcacag     60

atccagttgg tacagtctgg acctgagctg aagaagcctg gagagacagt caagatctcc    120

tgcaaggctt ctgggtatac cttcacaacc tatggaatga gctgggtgaa acaggctcca    180

ggaaagggtt taaagtggat gggctggata aacacctcct ctggagtgcc aacatatgct    240

gatgacttca tgggacggtt tgccttctct ttggaaacct ctgccagcac tgcctatttg    300

cagatcaaca acctcaaaaa tgaggacacg gctacgtatt tctgtgcaag agaccgctac    360

tacggggagg ttgcttactg gggccaaggg actctggtca ccgtctctgc agccaaaacg    420

acacccccat ctgtctatcc actggccccc ggatctgctg cccaaactaa ctccatggtg    480

accctgggat gcctggtcaa gggctatttc cctgagccag tgacagtgac ctggaactct    540

ggatccctgt ccagcggtgt gcacaccttc ccagctgtcc tgcagtctga cctctacact    600

ctgagcagct cagtgactgt cccctccagc acctggccca gcgagaccgt cacctgcaac    660

gttgcccacc cggccagcag caccaaggtg gacaagaaaa ttgtgcccag ggattgtggt    720

tgtaagcctt gcatatgtac agtcccagaa gtatcatctg tcttcatctt cccccaaag     780

cccaaggatg tgctcaccat tactctgact cctaaggtca cgtgtgttgt ggtagacatc    840
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agcaaggatg atcccgaggt ccagttcagc tggtttgtag atgatgtgga ggtgcacaca 900

gctcagacgc aaccccggga ggagcagttc aacagcactt tccgctcagt cagtgaactt 960

cccatcatgc atcaggactg gctcaatggc aaggagttca aatgcagggt caacagtgca 1020

gctttccctg cccccatcga gaaaaccatc tccaaaacca aaggcagacc gaaggctcca 1080

caggtgtaca ccattccacc tcccaaggag cagatggcca aggataaagt cagtctgacc 1140

tgcatgataa cagacttctt ccctgaagac attactgtgg agtggcagtg gaatgggcag 1200

ccagcggaga actacaagaa cactcagccc atcatggaca cagatggctc ttacttcgtc 1260

tacagcaagc tcaatgtgca gaagagcaac tgggaggcag gaaatacttt cacctgctct 1320

gtgttacatg agggcctgca caaccaccat actgagaaga gcctctccca ctctcctggt 1380

aaa 1383

<210> SEQ ID NO 279
<211> LENGTH: 461
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 279

Met Gly Trp Leu Trp Asn Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ala Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
20 25 30

Pro Gly Glu Thr Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Thr Tyr Gly Met Ser Trp Val Lys Gln Ala Pro Gly Lys Gly Leu
50 55 60

Lys Trp Met Gly Trp Ile Asn Thr Ser Ser Gly Val Pro Thr Tyr Ala
65 70 75 80

Asp Asp Phe Met Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser
85 90 95

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr
100 105 110

Tyr Phe Cys Ala Arg Asp Arg Tyr Tyr Gly Glu Val Ala Tyr Trp Gly
115 120 125

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

Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val
145 150 155 160

Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val
165 170 175

Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala
180 185 190

Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro
195 200 205

Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro
210 215 220

Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly
225 230 235 240

Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile
245 250 255

Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys
260 265 270

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Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln
        275                 280                 285

Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln
    290                 295                 300

Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu
305                 310                 315                 320

Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg
                325                 330                 335

Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
            340                 345                 350

Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro
        355                 360                 365

Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr
    370                 375                 380

Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln
385                 390                 395                 400

Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly
                405                 410                 415

Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu
            420                 425                 430

Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn
        435                 440                 445

His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys
    450                 455                 460


<210> SEQ ID NO 280
<211> LENGTH: 696
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 280

atggctccag tccaacttct agggcttttg ctgctctgcc tccgagccat gagatgtgac     60

atccagatga cccagtctcc ttcactcctg tcagcatctg tgggagacag agtcactctc    120

agctgcaaag caagtcagaa tatttacaag tacttaaact ggtatcagca aaagcttgga    180

gaagctccca aactcctgat atattataca aacagtttgc aaacgggcat cccatcaagg    240

ttcagtggca gtggatctgg tacagatttc acacttacca tcagcagcct gcagcctgaa    300

gatgttgcca catattactg ctatcagtat aacagtgggc ccacgtttgg agctgggacc    360

aagctggaac tgaaacgggc tgatgctgca ccaactgtat ctatcttccc accatccacg    420

gaacagttag caactggagg tgcctcagtc gtgtgcctca tgaacaactt ctatcccaga    480

gacatcagtg tcaagtggaa gattgatggc actgaacgac gagatggtgt cctggacagt    540

gttactgatc aggacagcaa agacagcacg tacagcatga gcagcaccct ctcgttgacc    600

aaggctgact atgaaagtca taacctctat acctgtgagg ttgttcataa gacatcatcc    660

tcacccgtcg tcaagagctt caacaggaat gagtgt                               696


<210> SEQ ID NO 281
<211> LENGTH: 232
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 281

Met Ala Pro Val Gln Leu Leu Gly Leu Leu Leu Leu Cys Leu Arg Ala
1               5                   10                  15
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Met Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Leu Leu Ser Ala
            20                  25                  30

Ser Val Gly Asp Arg Val Thr Leu Ser Cys Lys Ala Ser Gln Asn Ile
        35                  40                  45

Tyr Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Leu Gly Glu Ala Pro Lys
    50                  55                  60

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

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
                85                  90                  95

Leu Gln Pro Glu Asp Val Ala Thr Tyr Tyr Cys Tyr Gln Tyr Asn Ser
            100                 105                 110

Gly Pro Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp
        115                 120                 125

Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Thr Glu Gln Leu Ala
    130                 135                 140

Thr Gly Gly Ala Ser Val Val Cys Leu Met Asn Asn Phe Tyr Pro Arg
145                 150                 155                 160

Asp Ile Ser Val Lys Trp Lys Ile Asp Gly Thr Glu Arg Arg Asp Gly
                165                 170                 175

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

Met Ser Ser Thr Leu Ser Leu Thr Lys Ala Asp Tyr Glu Ser His Asn
        195                 200                 205

Leu Tyr Thr Cys Glu Val Val His Lys Thr Ser Ser Ser Pro Val Val
    210                 215                 220

Lys Ser Phe Asn Arg Asn Glu Cys
225                 230


<210> SEQ ID NO 282
<211> LENGTH: 1395
<212> TYPE: DNA
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 282

atgggcaggc ttacttcctc attcctgctg ctgattatcc ctgcatatgt cttgtctcag     60

gttactctga aagagtctgg ccctgggata ttgcagcctt cccagaccct cagtctgact    120

tgctctttct ctgggttttc actgagcact tctggtatat gtgtgagctg gattcgtcag    180

ccttcaggga agggtctgga gtggctggca actatttgtt gggaggatag taagggctac    240

aacccttctc tgaagaaccg gctcacaatc tccaaggaca cctccaacaa ccaagcattc    300

ctcaagatca ccagtgtgga cactgcagat accgccatat actactgtgc tcggcccctt    360

aactacggag ggtatagtga gctagaattg gattactggg gccaaggagt catggtcaca    420

gtctcctcag ctgaaacaac agccccatct gtctatccac tggctcctgg aactgctctc    480

aaaagtaact ccatggtgac cctgggatgc ctggtcaagg gctatttccc tgagccagtc    540

accgtgacct ggaactctgg agccctgtcc agcggtgtgc acaccttccc agctgtcctg    600

cagtctggac tctacactct caccagctca gtgactgtac cctccagcac ctggtccagc    660

caggccgtca cctgcaacgt agcccacccg gccagcagca ccaaggtgga caagaaaatt    720

gtgccaaggg aatgcaatcc ttgtggatgt acaggctcag aagtatcatc tgtcttcatc    780

ttcccccaa agaccaaaga tgtgctcacc atcactctga ctcctaaggt cacgtgtgtt    840
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gtggtagaca ttagccagaa tgatcccgag gtccggttca gctggtttat agatgacgtg 900

gaagtccaca cagctcagac tcatgccccg gagaagcagt ccaacagcac tttacgctca 960

gtcagtgaac tccccatcgt gcaccgggac tggctcaatg gcaagacgtt caaatgcaaa 1020

gtcaacagtg gagcattccc tgcccccatc gagaaaagca tctccaaacc cgaaggcaca 1080

ccacgaggtc cacaggtata caccatggcg cctcccaagg aagagatgac ccagagtcaa 1140

gtcagtatca cctgcatggt aaaaggcttc tatcccccag acatttatac ggagtggaag 1200

atgaacgggc agccacagga aaactacaag aacactccac ctacgatgga cacagatggg 1260

agttacttcc tctacagcaa gctcaatgta aagaaagaaa catggcagca gggaaacact 1320

ttcacgtgtt ctgtgctgca tgagggcctg cacaaccacc atactgagaa gagtctctcc 1380

cactctccgg gtaaa 1395

<210> SEQ ID NO 283
<211> LENGTH: 465
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 283

Met Gly Arg Leu Thr Ser Ser Phe Leu Leu Leu Ile Ile Pro Ala Tyr
1 5 10 15

Val Leu Ser Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln
20 25 30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu
35 40 45

Ser Thr Ser Gly Ile Cys Val Ser Trp Ile Arg Gln Pro Ser Gly Lys
50 55 60

Gly Leu Glu Trp Leu Ala Thr Ile Cys Trp Glu Asp Ser Lys Gly Tyr
65 70 75 80

Asn Pro Ser Leu Lys Asn Arg Leu Thr Ile Ser Lys Asp Thr Ser Asn
85 90 95

Asn Gln Ala Phe Leu Lys Ile Thr Ser Val Asp Thr Ala Asp Thr Ala
100 105 110

Ile Tyr Tyr Cys Ala Arg Pro Leu Asn Tyr Gly Gly Tyr Ser Glu Leu
115 120 125

Glu Leu Asp Tyr Trp Gly Gln Gly Val Met Val Thr Val Ser Ser Ala
130 135 140

Glu Thr Thr Ala Pro Ser Val Tyr Pro Leu Ala Pro Gly Thr Ala Leu
145 150 155 160

Lys Ser Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ala Leu Ser Ser Gly
180 185 190

Val His Thr Phe Pro Ala Val Leu Gln Ser Gly Leu Tyr Thr Leu Thr
195 200 205

Ser Ser Val Thr Val Pro Ser Ser Thr Trp Ser Ser Gln Ala Val Thr
210 215 220

Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile
225 230 235 240

Val Pro Arg Glu Cys Asn Pro Cys Gly Cys Thr Gly Ser Glu Val Ser
245 250 255

Ser Val Phe Ile Phe Pro Pro Lys Thr Lys Asp Val Leu Thr Ile Thr
260 265 270

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Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Gln Asn Asp
        275                 280                 285

Pro Glu Val Arg Phe Ser Trp Phe Ile Asp Asp Val Glu Val His Thr
    290                 295                 300

Ala Gln Thr His Ala Pro Glu Lys Gln Ser Asn Ser Thr Leu Arg Ser
305                 310                 315                 320

Val Ser Glu Leu Pro Ile Val His Arg Asp Trp Leu Asn Gly Lys Thr
                325                 330                 335

Phe Lys Cys Lys Val Asn Ser Gly Ala Phe Pro Ala Pro Ile Glu Lys
            340                 345                 350

Ser Ile Ser Lys Pro Glu Gly Thr Pro Arg Gly Pro Gln Val Tyr Thr
        355                 360                 365

Met Ala Pro Pro Lys Glu Glu Met Thr Gln Ser Gln Val Ser Ile Thr
    370                 375                 380

Cys Met Val Lys Gly Phe Tyr Pro Pro Asp Ile Tyr Thr Glu Trp Lys
385                 390                 395                 400

Met Asn Gly Gln Pro Gln Glu Asn Tyr Lys Asn Thr Pro Pro Thr Met
                405                 410                 415

Asp Thr Asp Gly Ser Tyr Phe Leu Tyr Ser Lys Leu Asn Val Lys Lys
            420                 425                 430

Glu Thr Trp Gln Gln Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu
        435                 440                 445

Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly
    450                 455                 460

Lys
465


<210> SEQ ID NO 284
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(6)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 284

Val Ile Xaa Tyr Xaa Xaa Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1               5                   10                  15

Gly


<210> SEQ ID NO 285
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(11)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<222> LOCATION: (13)..(15)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(17)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 285

Trp Ile Xaa Ala Xaa Asn Gly Xaa Xaa Xaa Xaa Ala Xaa Xaa Xaa Gln
1 5 10 15

Xaa

<210> SEQ ID NO 286
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 286

Ala Gln Glu Gly Xaa Ala Pro Asp Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 287
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 287

Gln Ala Trp Tyr Ser Ser Thr Asn Val Xaa
1 5 10

<210> SEQ ID NO 288
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (9)..(10)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 288

Gln Ala Trp Asp Ser Ser Thr Ala Xaa Xaa
1 5 10

<210> SEQ ID NO 289
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(11)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

<400> SEQUENCE: 289

Gln Ser Asp Tyr Ser Ser Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> SEQ ID NO 290
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 290

cagtctgtgc tgactcagcc accctcaacg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttctg gaagcaactc caacatcgga agtcaaactg ttaactggta ccagcaactc 120

ccaggaacgg cccccaaact cctcatcttt agtcatcatc accggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag 240

tctgaggatg aggctgatta ttactgtgca gcatgggatg acagcctgaa tggtgtggta 300

ttcggcggag ggaccaaact gaccgtccta 330

<210> SEQ ID NO 291
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

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

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

Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Phe Ser His His His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Gly Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 292
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 292

gaggtgcagc tggtggagtc tgggggaggc ttggtaaagc ctgggggtc ccttagactc 60

tcctgtgcag cctctggatt cactttcagt gacgcctgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggttggccgt attaaaagca aaactgatgg tgggacaaca 180

gacttcgctg cacccgtgaa aggcagattc accatctcaa gagatgattc aaaaaacacg 240

ctgtatctgc aaatgaacag cctgaacacc gaggacacag cagtgtatta ctgtacctca 300

tctcatagca gcgcctggta cggctacttc ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 293
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
20 25 30

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

Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Phe Ala Ala
    50                  55                  60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Asn Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Thr Ser Ser His Ser Ser Ala Trp Tyr Gly Tyr Phe Gly Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210> SEQ ID NO 294
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

Ser Gly Ser Asn Ser Asn Ile Gly Ser Gln Thr Val Asn
1               5                   10


<210> SEQ ID NO 295
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

Ser His His His Arg Pro Ser
1               5


<210> SEQ ID NO 296
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 296

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1               5                   10


<210> SEQ ID NO 297
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

Gly Phe Thr Phe Ser Asp Ala Trp Met Ser
1               5                   10


<210> SEQ ID NO 298
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Phe Ala Ala Pro
1               5                   10                  15

Val Lys Gly


<210> SEQ ID NO 299
<211> LENGTH: 14
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 299

Ser His Ser Ser Ala Trp Tyr Gly Tyr Phe Gly Met Asp Val
1 5 10

<210> SEQ ID NO 300
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

cagtctgtgc tgactctgtc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttctg gaagcacctc caacatcgga agtaatactg taaattggtt ccagcagctc 120

ccaggaacgg cccccaaact cctcatcttt agtaataatc agcggccctc aggggtccct 180

gaccgatttt ctgcctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag 240

tctgaggatg aggctgatta ttactgtgca gcgtgggatg acagcctgaa tggtgtggta 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 301
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Thr Ser Asn Ile Gly Ser Asn
20 25 30

Thr Val Asn Trp Phe Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Phe Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Ala Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Gly Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 302
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

gaggtgcagc tggtggagtc tgggggaggc ttggtaaagc ctgggggtc ccttagactc 60

tcctgtgcag cctctggaat cactttcagt aacgcctgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggttggccgt atcaaaagca agactgatga tgggacaaca 180

gactacgctg cacccgtgaa aggcagattc accatctcaa gagatgattc aaaaaacacg 240

ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatta ctgtaccaca 300

tctgatagca gcggctggta cggctactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 303
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Ile Thr Phe Ser Asn Ala
20 25 30

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

Gly Arg Ile Lys Ser Lys Thr Asp Asp Gly Thr Thr Asp Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Thr Thr Ser Asp Ser Ser Gly Trp Tyr Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 304
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

Ser Gly Ser Thr Ser Asn Ile Gly Ser Asn Thr Val Asn
1 5 10

<210> SEQ ID NO 305
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

Ser Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 306
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 307
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

Gly Ile Thr Phe Ser Asn Ala Trp Met Ser
1 5 10

<210> SEQ ID NO 308
<211> LENGTH: 19

<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

Arg Ile Lys Ser Lys Thr Asp Asp Gly Thr Thr Asp Tyr Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> SEQ ID NO 309
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

Ser Asp Ser Ser Gly Trp Tyr Gly Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 310
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310

cagtctgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttttg gaagcagctc caacatcgga agtaattctg taaactggta ccagcagctc 120

ccaggaacgg cccccaaact cctcatcttt agtaatgatc agcggccctc aggggtccct 180

gaccgattct ctgggtccaa gtctggcacc tcagattccc tggccatcag tgggctccag 240

tctgaggatg aagctgatta ttactgtgca gcatgggatg acagcctgaa tggtgtggta 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 311
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

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

Arg Val Thr Ile Ser Cys Phe Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

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

Ile Phe Ser Asn Asp Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Asp Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95

Asn Gly Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 312
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 312

gaggtgcagc tggtggagtc tgggggaggc ttggtaaagc ctgggggGTC ccttagactc 60

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tcctgtgcag cctctggatt cactttcagt aatgcctgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggttggccgt attaaaagca aaactgatgg tgggacaaca 180

gactacgctg ctcccgtgaa aggcagattc accatctcaa gagatgattc aaaagacacg 240

ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatta ctgtaccaca 300

tctgatagca gcggctggtt cgggtactac ggaatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 313
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 313

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Ala
20 25 30

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

Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asp Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Thr Thr Ser Asp Ser Ser Gly Trp Phe Gly Tyr Tyr Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 314
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 314

Phe Gly Ser Ser Ser Asn Ile Gly Ser Asn Ser Val Asn
1 5 10

<210> SEQ ID NO 315
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 315

Ser Asn Asp Gln Arg Pro Ser
1 5

<210> SEQ ID NO 316
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 316

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 317
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

Gly Phe Thr Phe Ser Asn Ala Trp Met Ser
1 5 10

<210> SEQ ID NO 318
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Tyr Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> SEQ ID NO 319
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319

Ser Asp Ser Ser Gly Trp Phe Gly Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 320
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320

cagtctgtgc tgactcagcc accctcaacg tctgggaccc ccgggcagag ggtcaccatc 60

tcttgttttg gaagcaactc caacatcgga agtcaaactg ttaactggta ccagcaactc 120

ccaggaacgg cccccaaact cctcatcttt agtcatcatc accggccctc aggggtccct 180

gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tgggctccag 240

tctgaggatg aggctgatta ttactgtgca acatgggatg acagcctgaa tggtgtggta 300

ttcggcggag ggaccaaact gaccgtccta 330

<210> SEQ ID NO 321
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

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

Arg Val Thr Ile Ser Cys Phe Gly Ser Asn Ser Asn Ile Gly Ser Gln
20 25 30

Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Phe Ser His His His Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Asp Asp Ser Leu
85 90 95

-continued

Asn Gly Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 322
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

gaggtgcagc tggtggagtc tgggggaggc ttggtaaagc ctgggggtc ccttagactc 60

tcctgtgcag cctctggatt cactttcagt gacgcctgga tgagctgggt ccgccaggct 120

ccagggaagg gactggggtg ggttggccgt attaaaagca aaactgatgg tgggacaaca 180

gacttcgctg cacccgtgaa aggcagattc accatctcaa gagatgattc aaaaaacacg 240

ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatta ctgtacctca 300

tctcatagca gcgcctggta cggctacttc ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 323
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 323

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Ala
20 25 30

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

Gly Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Phe Ala Ala
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Thr Ser Ser His Ser Ser Ala Trp Tyr Gly Tyr Phe Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 324
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

Phe Gly Ser Asn Ser Asn Ile Gly Ser Gln Thr Val Asn
1 5 10

<210> SEQ ID NO 325
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 325

Ser His His His Arg Pro Ser
1 5

<210> SEQ ID NO 326
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 326

Ala Thr Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 327
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

Gly Phe Thr Phe Ser Asp Ala Trp Met Ser
1 5 10

<210> SEQ ID NO 328
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 328

Arg Ile Lys Ser Lys Thr Asp Gly Gly Thr Thr Asp Phe Ala Ala Pro
1 5 10 15

Val Lys Gly

<210> SEQ ID NO 329
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 329

Ser His Ser Ser Ala Trp Tyr Gly Tyr Phe Gly Met Asp Val
1 5 10

<210> SEQ ID NO 330
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 330

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag taatgttggg agttataacc ttgtctcctg gtaccaacag 120

cacccaggca aagcccccaa actcatgatt tctgaggtca gtaagcggcc ctcaggactt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggctga ttattactgc tgctcatatg caggtagtag cactttaata 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 331
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 331

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Val Gly Ser Tyr

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```
            20                  25                  30

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

Met Ile Ser Glu Val Ser Lys Arg Pro Ser Gly Leu Ser Asn Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser
                85                  90                  95

Ser Thr Leu Ile Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110


<210> SEQ ID NO 332
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

caggtgcagc tacagcagtg gggcgcagga ccgttgaagc cttcggagac cctgtccctc     60

acctgcgctg tctataatgg gtccttcagt ggttactact ggagctggat ccgccagccc    120

ccagggaagg ggctggaatg gattggggat atcaatcata gtggaaacac caagtacaac    180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaatca gttctccctg    240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggcgatttt    300

tggagtggtt ttgactggtt cgacccctgg ggccagggaa ccctggtcac cgtctcctca    360


<210> SEQ ID NO 333
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

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

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

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

Gly Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 334
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Leu Val Ser
1               5                   10
```

<210> SEQ ID NO 335
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

Glu Gly Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 336
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 336

Cys Ser Tyr Ala Gly Ser Ser Thr Leu Ile
1 5 10

<210> SEQ ID NO 337
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337

Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
1 5 10

<210> SEQ ID NO 338
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 338

Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 339
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 339

Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro
1 5 10

<210> SEQ ID NO 340
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 340

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag taatgttggg acttataaac ttgtctcctg gtaccaacag 120

cacccaggca aagcccccaa actcatgatt tctgaggtca gtaagcggcc ctcaggactt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggctga ttattactgc tcctcatatg caggtgatag cactttggta 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 341
<211> LENGTH: 110

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Val Gly Thr Tyr
20 25 30

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

Met Ile Ser Glu Val Ser Lys Arg Pro Ser Gly Leu Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Gly Asp
85 90 95

Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 342
<211> LENGTH: 359
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

caggtgcacc tacagcagtg gggcgcagga ccgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctacaatgg gtccttcagt ggttactatt ggagctggat ccgccagccc 120

ccagggaagg ggctggattg gattggggat atcaatcata gtggaaacac caagtacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgg ccaagaatca gttctccctg 240

aagctgagtt ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggcgatttt 300

tggagtggtt ttgactggtt cgacccctgg ggccagggaa ccctggtcac cgtctcctc 359

<210> SEQ ID NO 343
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 343

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

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

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

Gly Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

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<210> SEQ ID NO 344
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 344

Thr Gly Thr Ser Ser Asn Val Gly Thr Tyr Lys Leu Val Ser
1 5 10

<210> SEQ ID NO 345
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

Glu Val Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 346
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

Ser Ser Tyr Ala Gly Asp Ser Thr Leu Val
1 5 10

<210> SEQ ID NO 347
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 347

Asn Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
1 5 10

<210> SEQ ID NO 348
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 348

Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 349
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 349

Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro
1 5 10

<210> SEQ ID NO 350
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 350

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag taatgttggg agttataacc ttgtctcctg gtaccaacaa 120

cacccaggca aagcccccaa actcatgctt tctgaggtca gtaagcggcc ctcaggactt 180

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tctagtcgct tctctggctc caagtctggc gacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggctga ttattactgc tgctcatatg caggtagtag cactttggta 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 351
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 351

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Val Gly Ser Tyr
20 25 30

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

Met Leu Ser Glu Val Ser Lys Arg Pro Ser Gly Leu Ser Ser Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asp Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 352
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

caggtgcagc tacagcagtg gggcgcagga ccgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggaatg gattggggat atcaatcata gtggaaacac caagtacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaatca gttctccctg 240

aagctgaact ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggcgatttt 300

tggagtggtt ttgactggtt cgacccctgg ggccagggaa ccctggtcac cgtctcttct 360

<210> SEQ ID NO 353
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

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

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

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

Gly Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys
50 55 60

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

Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala

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                85                  90                  95

Arg Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 354
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 354

Thr Gly Thr Ser Ser Asn Val Gly Ser Tyr Asn Leu Val Ser
1               5                   10


<210> SEQ ID NO 355
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

Glu Val Ser Lys Arg Pro Ser
1               5


<210> SEQ ID NO 356
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

Cys Ser Tyr Ala Gly Ser Ser Thr Leu Val
1               5                   10


<210> SEQ ID NO 357
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
1               5                   10


<210> SEQ ID NO 358
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys Ser
1               5                   10                  15


<210> SEQ ID NO 359
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro
1               5                   10


<210> SEQ ID NO 360
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
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<400> SEQUENCE: 360

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag taatgttggg agttataacc ttgtctcctg gtaccaaaag 120

cacccaggca aagcccccaa actcatgatt tctgaggtca gtaagcggcc ctcaggactt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggctga ttattactgc tgctcatatg caggtagtag tactttggta 300

ttcggcggag ggaccaaact gaccgtccta 330

<210> SEQ ID NO 361
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 361

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Val Gly Ser Tyr
20 25 30

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

Met Ile Ser Glu Val Ser Lys Arg Pro Ser Gly Leu Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser
85 90 95

Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 362
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

caggtgcagc tacagcagtg gggcgcagga ccgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggaatg gattggggat atcaatcata gtggaaacac caagtacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaaaaatca tttctccctg 240

aagctgagtt ctgtgaccgc cgcggacacg gctgtgtatt actgtgcaag aggcgatttt 300

tggagtggtt ttgactggtt cgacccctgg ggccagggaa ccctggtcac cgtctcctca 360

<210> SEQ ID NO 363
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

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

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

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile

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        35                  40                  45

Gly Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 364
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

Thr Gly Thr Ser Ser Asn Val Gly Ser Tyr Asn Leu Val Ser
1               5                   10


<210> SEQ ID NO 365
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 365

Glu Val Ser Lys Arg Pro Ser
1               5


<210> SEQ ID NO 366
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

Cys Ser Tyr Ala Gly Ser Ser Thr Leu Val
1               5                   10


<210> SEQ ID NO 367
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
1               5                   10


<210> SEQ ID NO 368
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 368

Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys Ser
1               5                   10                  15


<210> SEQ ID NO 369
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 369
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Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp
1 5 10

<210> SEQ ID NO 370
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 370

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag taatgttggg acttataaac ttgtctcctg gtaccaacag 120

cacccagaca aagcccccaa actcattatt tctgaggtca gtaagcggcc ctcaggactt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggttga ttattactgc tcctcatatg caggtgatag cactttggta 300

ttcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 371
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 371

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Val Gly Thr Tyr
20 25 30

Lys Leu Val Ser Trp Tyr Gln Gln His Pro Asp Lys Ala Pro Lys Leu
35 40 45

Ile Ile Ser Glu Val Ser Lys Arg Pro Ser Gly Leu Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Val Asp Tyr Tyr Cys Ser Ser Tyr Ala Gly Asp
85 90 95

Ser Thr Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 372
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 372

caggtgcacc tacagcagtg gggcgcagga ccgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctataatgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggaatg gattggggat atcaatcata gtggaaacac caagtacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgg ccaagaatca gttctccctg 240

aagctgagtt ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggcgatttt 300

tggagtggtt ttgactggtt cgacccctgg ggccagggaa ccctggtcac cgtctcctcc 360

<210> SEQ ID NO 373
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 373

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

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

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

Gly Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys
50 55 60

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

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 374
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 374

Thr Gly Thr Ser Ser Asn Val Gly Thr Tyr Lys Leu Val Ser
1 5 10

<210> SEQ ID NO 375
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 375

Glu Val Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 376
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

Cys Ser Ser Tyr Ala Gly Asp Ser Thr Leu Val
1 5 10

<210> SEQ ID NO 377
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

Asn Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
1 5 10

<210> SEQ ID NO 378
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys Ser

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1 5 10 15

<210> SEQ ID NO 379
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp
1 5 10

<210> SEQ ID NO 380
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 380

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60

tcctgcactg gaaccagcag taatgttggg acttataagc ttgtctcctg gtaccaacaa 120

cacccaggca aagcccccaa actcatgatt tctgaggtca gtaagcggcc ctcaggactt 180

tctaatcgct tctctggctc caagtctggc aacacggcct ccctgacaat ctctgggctc 240

caggctgagg acgaggctga ttattactgc tcctcatatg caggtgatag cactttgata 300

gtcggcggag ggaccaagct gaccgtccta 330

<210> SEQ ID NO 381
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asn Val Gly Thr Tyr
20 25 30

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

Met Ile Ser Glu Val Ser Lys Arg Pro Ser Gly Leu Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Gly Asp
85 90 95

Ser Thr Leu Ile Val Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 382
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 382

caggtgcacc tacaacagtg gggcgcagga ccgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctataatgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggaatg gattggggat atcaatcata gtggaaacac caagtacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgg ccaagaatca gttctccctg 240

aagctgaatt ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggcgatttt 300

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tggagtggtt ttgactggtt cgacccctgg ggccagggaa ccctggtcac cgtctcttca 360

<210> SEQ ID NO 383
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 383

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

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

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

Gly Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys
50 55 60

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

Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 384
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 384

Thr Gly Thr Ser Ser Asn Val Gly Thr Tyr Lys Leu Val Ser
1 5 10

<210> SEQ ID NO 385
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 385

Glu Val Ser Lys Arg Pro Ser
1 5

<210> SEQ ID NO 386
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 386

Cys Ser Ser Tyr Ala Gly Asp Ser Thr Leu Ile
1 5 10

<210> SEQ ID NO 387
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 387

Asn Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
1 5 10

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<210> SEQ ID NO 388
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 388

Asp Ile Asn His Ser Gly Asn Thr Lys Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 389
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 389

Gly Asp Phe Trp Ser Gly Phe Asp Trp Phe Asp Pro
1 5 10

<210> SEQ ID NO 390
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 390

cagtctgtgc tgacgcagcc gccctcagtg tctggggccc cagggcagag ggtcaccatc 60

tcctgcactg ggagcagctc caacatcggg gcaggttatg gtgtatactg gtaccagcag 120

cttccaggaa cagcccccaa actcctcatc tatggtcaca acaatcggcc ctcaggggtc 180

cctgaccgat tctctggctc caagtctgac acctcagcct ccctggccat cactgggctc 240

caggctgaag atgaggctga ttattactgc cagtcctatg acagcaacct gattggttct 300

gtcttcggaa ctgggaccaa ggtcaccgtc cta 333

<210> SEQ ID NO 391
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

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

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

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

Leu Ile Tyr Gly His Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Asp Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Asn
85 90 95

Leu Ile Gly Ser Val Phe Gly Thr Gly Thr Lys Val Thr Val Leu
100 105 110

<210> SEQ ID NO 392
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 392

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caggttcagc tggtgcagtc tggagctgag gtgaaggaac ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggtta cacctttacc agctatggtg tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacactctat 180

gcacagcacc tcctgggcag agtcaccatg accacagaca catccacgag cacagcctac 240

atggagctga ggagcctgag atctgacgac acggccgtat attattgtgc gagagaggat 300

ttggggatgg gtgactactg gggccaggga accctggtca ccgtctcctc a 351

<210> SEQ ID NO 393
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 393

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

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

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

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Leu Tyr Ala Gln His Leu
50 55 60

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

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

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

Val Thr Val Ser Ser
115

<210> SEQ ID NO 394
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Gly Val Tyr
1 5 10

<210> SEQ ID NO 395
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

Gly His Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 396
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

Gln Ser Tyr Asp Ser Asn Leu Ile Gly Ser Val
1 5 10

<210> SEQ ID NO 397

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<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

Gly Tyr Thr Phe Thr Ser Tyr Gly Val Ser
1 5 10

<210> SEQ ID NO 398
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

Trp Ile Ser Ala Tyr Asn Gly Asn Thr Leu Tyr Ala Gln His Leu Leu
1 5 10 15

Gly

<210> SEQ ID NO 399
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

Glu Asp Leu Gly Met Gly Asp Tyr
1 5

<210> SEQ ID NO 400
<211> LENGTH: 362
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

Met Gly Val Pro Arg Pro Gln Pro Trp Ala Leu Gly Leu Leu Leu Phe
1 5 10 15

Leu Leu Pro Gly Ser Leu Gly Ala Glu Ser His Leu Ser Leu Leu Tyr
20 25 30

His Leu Thr Ala Val Ser Ser Pro Ala Pro Gly Thr Pro Ala Phe Trp
35 40 45

Val Ser Gly Trp Leu Gly Pro Gln Gln Tyr Leu Ser Tyr Asn Ser Leu
50 55 60

Arg Gly Glu Ala Glu Pro Cys Gly Ala Trp Val Trp Glu Asn Gln Val
65 70 75 80

Ser Trp Tyr Trp Glu Lys Glu Thr Thr Asp Leu Arg Ile Lys Glu Lys
85 90 95

Leu Phe Leu Glu Ala Phe Lys Ala Leu Gly Gly Lys Gly Pro Tyr Thr
100 105 110

Leu Gln Gly Leu Leu Gly Cys Glu Leu Gly Pro Asp Asn Thr Ser Val
115 120 125

Pro Thr Ala Lys Phe Ala Leu Asn Gly Glu Glu Phe Met Asn Phe Asp
130 135 140

Leu Lys Gln Gly Thr Trp Gly Gly Asp Trp Pro Glu Ile Ser Gln Arg
145 150 155 160

Trp Gln Gln Gln Asp Lys Ala Ala Asn Lys Glu Leu Thr Phe Leu Leu
165 170 175

Phe Ser Cys Pro His Arg Leu Arg Glu His Leu Glu Arg Gly Arg Gly
180 185 190

Asn Leu Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro
195 200 205

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Ser Ser Pro Gly Phe Ser Val Leu Thr Cys Ser Ala Phe Ser Phe Tyr
    210                 215                 220

Pro Pro Glu Leu Gln Leu Arg Phe Leu Arg Asn Gly Leu Ala Ala Gly
225                 230                 235                 240

Thr Gly Gln Gly Asp Phe Gly Pro Asn Ser Asp Gly Ser Phe His Ala
                245                 250                 255

Ser Ser Ser Leu Thr Val Lys Ser Gly Asp Glu His His Tyr Cys Cys
            260                 265                 270

Ile Val Gln His Ala Gly Leu Ala Gln Pro Leu Arg Val Glu Leu Glu
        275                 280                 285

Ser Pro Ala Lys Ser Ser Val Leu Val Val Gly Ile Val Ile Gly Val
    290                 295                 300

Leu Leu Leu Thr Ala Ala Ala Val Gly Gly Ala Leu Leu Trp Arg Arg
305                 310                 315                 320

Met Arg Ser Gly Leu Pro Ala Pro Trp Ile Ser Leu Arg Gly Asp Asp
                325                 330                 335

Thr Gly Val Leu Leu Pro Thr Pro Gly Glu Ala Gln Asp Ala Asp Leu
            340                 345                 350

Lys Asp Val Asn Val Ile Pro Ala Thr Ala
        355                 360
```

<210> SEQ ID NO 401
<211> LENGTH: 990
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

```
gcctccacca agggcccatc ggtcttcccc ctggcaccct cctccaagag cacctctggg     60

ggcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg    120

tggaactcag gcgccctgac cagcggcgtg cacaccttcc cggctgtcct acagtcctca    180

ggactctact ccctcagcag cgtggtgacc gtgccctcca gcagcttggg cacccagacc    240

tacatctgca acgtgaatca caagcccagc aacaccaagg tggacaagaa agttgagccc    300

aaatcttgtg acaaaactca cacatgccca ccgtgcccag cacctgaact cctgggggga    360

ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc tcatgatctc ccggaccccct    420

gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc ctgaggtcaa gttcaactgg    480

tacgtggacg gcgtggaggt gcataatgcc aagacaaagc cgcgggagga gcagtacaac    540

agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc aggactggct gaatggcaag    600

gagtacaagt gcaaggtctc caacaaagcc ctcccagccc ccatcgagaa aaccatctcc    660

aaagccaaag ggcagccccg agaaccacag gtgtacaccc tgcccccatc ccgggatgag    720

ctgaccaaga accaggtcag cctgacctgc ctggtcaaag gcttctatcc cagcgacatc    780

gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctcccgtg    840

ctggactccg acggctcctt cttcctctat agcaagctca ccgtggacaa gagcaggtgg    900

cagcagggga acgtcttctc atgctccgtg atgcatgagg ctctgcacaa ccactacacg    960

cagaagagcc tctccctgtc tccgggtaaa                                     990
```

<210> SEQ ID NO 402
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 402

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

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

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

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
325 330

<210> SEQ ID NO 403
<211> LENGTH: 978
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403

gcctccacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag 60

agcacagcgg ccctgggctg cctggtcaag gactacttcc ccgaaccggt gacggtgtcg 120

tggaactcag gcgctctgac cagcggcgtg cacaccttcc cagctgtcct acagtcctca 180

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ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg cacccagacc    240

tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc    300

aaatgttgtg tcgagtgccc accgtgccca gcaccacctg tggcaggacc gtcagtcttc    360

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacgtgc    420

gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc    480

gtggaggtgc ataatgccaa gacaaagcca cgggaggagc agttcaacag cacgttccgt    540

gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc    600

aaggtctcca acaaaggcct cccagccccc atcgagaaaa ccatctccaa aaccaaaggg    660

cagccccgag aaccacaggt gtacaccctg cccccatccc gggaggagat gaccaagaac    720

caggtcagcc tgacctgcct ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg    780

gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac    840

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac    900

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc    960

tccctgtctc cgggtaaa                                                  978
```

<210> SEQ ID NO 404
<211> LENGTH: 326
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

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

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

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

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
        195                 200                 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
    210                 215                 220

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

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                245                 250                 255

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            260                 265                 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        275                 280                 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    290                 295                 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305                 310                 315                 320

Ser Leu Ser Pro Gly Lys
                325


<210> SEQ ID NO 405
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

cgaactgtgg ctgcaccatc tgtcttcatc ttcccgccat ctgatgagca gttgaaatct     60

ggaactgcct ctgttgtgtg cctgctgaat aacttctatc ccagagaggc caaagtacag    120

tggaaggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac    180

agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag    240

aaacacaaag tctacgcctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag    300

agcttcaaca ggggagagtg t                                              321


<210> SEQ ID NO 406
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
1               5                   10                  15

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
            20                  25                  30

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
        35                  40                  45

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
    50                  55                  60

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
65                  70                  75                  80

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
                85                  90                  95

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105


<210> SEQ ID NO 407
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 407

ggtcagccca aggccaaccc cactgtcact ctgttcccgc cctcctctga ggagctccaa     60
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gccaacaagg ccacactagt gtgtctgatc agtgacttct acccgggagc tgtgacagtg 120

gcctggaagg cagatggcag ccccgtcaag gcgggagtgg agaccaccaa accctccaaa 180

cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcccga gcagtggaag 240

tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctacag aatgttca 318

<210> SEQ ID NO 408
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
100 105

<210> SEQ ID NO 409
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409

ggtcagccca aggctgcccc ctcggtcact ctgttcccgc cctcctctga ggagcttcaa 60

gccaacaagg ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg 120

gcctggaagg cagatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa 180

caaagcaaca acaagtacgc ggccagcagc tatctgagcc tgacgcctga gcagtggaag 240

tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctacag aatgttca 318

<210> SEQ ID NO 410
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
35 40 45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

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Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65                  70                  75                  80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
                85                  90                  95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
            100                 105


<210> SEQ ID NO 411
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 411

ggtcagccca aggctgcccc ctcggtcact ctgttcccac cctcctctga ggagcttcaa     60

gccaacaagg ccacactggt gtgtctcata agtgacttct acccgggagc cgtgacagtg    120

gcctggaagg cagatagcag ccccgtcaag gcgggagtgg agaccaccac accctccaaa    180

caaagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga gcagtggaag    240

tcccacaaaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg    300

gcccctacag aatgttca                                                  318


<210> SEQ ID NO 412
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
            20                  25                  30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro
        35                  40                  45

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
    50                  55                  60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65                  70                  75                  80

Ser His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
                85                  90                  95

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
            100                 105


<210> SEQ ID NO 413
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 413

ggtcagccca aggctgcccc atcggtcact ctgttcccgc cctcctctga ggagcttcaa     60

gccaacaagg ccacactggt gtgcctgatc agtgacttct acccgggagc tgtgaaagtg    120

gcctggaagg cagatggcag ccccgtcaac acgggagtgg agaccaccac accctccaaa    180

cagagcaaca acaagtacgc ggccagcagc tacctgagcc tgacgcctga gcagtggaag    240

tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg    300

gcccctgcag aatgtgca                                                  318
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-continued

<210> SEQ ID NO 414
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 414

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Lys Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

Val Asn Thr Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Ala Glu Cys Ala
100 105

<210> SEQ ID NO 415
<211> LENGTH: 318
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 415

ggtcagccca aggctgcccc ctcggtcact ctgttcccac cctcctctga ggagcttcaa 60

gccaacaagg ccacactggt gtgtctcgta agtgacttct acccgggagc cgtgacagtg 120

gcctggaagg cagatggcag ccccgtcaag gtgggagtgg agaccaccaa accctccaaa 180

caaagcaaca acaagtatgc ggccagcagc tacctgagcc tgacgcccga gcagtggaag 240

tcccacagaa gctacagctg ccgggtcacg catgaaggga gcaccgtgga gaagacagtg 300

gcccctgcag aatgctct 318

<210> SEQ ID NO 416
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 416

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Val Ser Asp
20 25 30

Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro
35 40 45

Val Lys Val Gly Val Glu Thr Thr Lys Pro Ser Lys Gln Ser Asn Asn
50 55 60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
65 70 75 80

Ser His Arg Ser Tyr Ser Cys Arg Val Thr His Glu Gly Ser Thr Val
85 90 95

Glu Lys Thr Val Ala Pro Ala Glu Cys Ser
100 105

What is claimed:

1. An isolated antibody comprising SEQ ID NOs: 334-339 wherein the antibody binds to human hepcidin of SEQ ID NO: 9 with an affinity K_D of less than about 10^{-8}M and which exhibits at least one of the properties selected from the group consisting of:

(a) at least about a 50-fold higher K_D at a pH of about 5.5 compared to its K_D for said hepcidin at a pH of about 7.4;

(b) at least about a 5-fold faster clearance of said hepcidin compared to antibody 1S1 having the heavy chain variable region of SEQ ID NO: 202 and the light chain variable region of SEQ ID NO: 128; and

(c) an off rate of about 6×10^{-2} s^{-1} or higher at about pH 5.5.

2. An isolated antibody comprising the amino acid sequence SEQ ID NOs: 334-339 that binds to human hepcidin of SEQ ID NO: 9, with an affinity K_D of at least 10^{-8}M and said antibody has at least about a 50-fold higher K_D at about pH 5.5 compared to its K_D for said hepcidin at about pH 7.4 or said antibody has an off rate of about 6×10^{-2} s^{-1} or higher at about pH 5.5, wherein said antibody is obtained by:

(a) replacing an amino acid in the heavy or light chain of said antibody with a histidine;

(b) screening the antibody obtained in (a) for differential pH binding;

(c) replacing another amino acid in the heavy or light chain of said antibody with a histidine; and

(d) screening said antibody for having at least one of the properties selected from the group consisting of:

(i) at least about 50-fold higher K_D at about pH 5.5 compared to its K_D for said hepcidin at about pH 7.4; and

(ii) an off rate of about 6×10^{-2} s^{-1} or higher at about pH 5.5.

* * * * *