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Ober et al.

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(45) **Date of Patent: Oct. 4, 2022**

(54) **FUSION PROTEINS (SELDEGS) FOR SELECTIVELY DEPLETING ANTIGEN-SPECIFIC ANTIBODIES AND METHODS OF USE THEREOF**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 247 days.

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§ 371 (c)(1),
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PCT Pub. Date: **Jun. 7, 2018**

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Related U.S. Application Data

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(51) **Int. Cl.**

C07K 16/28	(2006.01)
A61K 38/00	(2006.01)
C07K 14/71	(2006.01)
A61K 51/10	(2006.01)

(52) **U.S. Cl.**
CPC ***C07K 16/2881*** (2013.01); ***C07K 14/71*** (2013.01); *A61K 38/00* (2013.01); *A61K 51/1027* (2013.01); *C07K 2317/52* (2013.01); *C07K 2317/569* (2013.01); *C07K 2317/71* (2013.01); *C07K 2317/72* (2013.01); *C07K 2317/76* (2013.01); *C07K 2317/77* (2013.01); *C07K 2317/92* (2013.01); *C07K 2319/30* (2013.01)

(58) **Field of Classification Search**
CPC C07K 16/2881; C07K 14/71; C07K 2317/52; C07K 2317/569; C07K 2317/71; C07K 2317/72; C07K 2317/76; C07K 2317/77; C07K 2317/92; C07K 2319/30; A61K 38/00
See application file for complete search history.

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Primary Examiner — Robert S Landsman
(74) *Attorney, Agent, or Firm* — Edell, Shapiro & Finnan, LLC

(57) **ABSTRACT**

The present disclosure includes a fusion protein, called a "Seldeg", including a targeting component that specifically binds to a cell surface receptor or other cell surface molecule at near-neutral pH, and an antigen component fused directly or indirectly to the targeting component. The antigen component is configured to specifically bind a target antigen-specific antibody. The present disclosure also includes a method of depleting a target antigen-specific antibody from a patient by administering to the patient a Seldeg having an antigen component configured to specifically bind the target antigen-specific antibody.

20 Claims, 19 Drawing Sheets

Specification includes a Sequence Listing.

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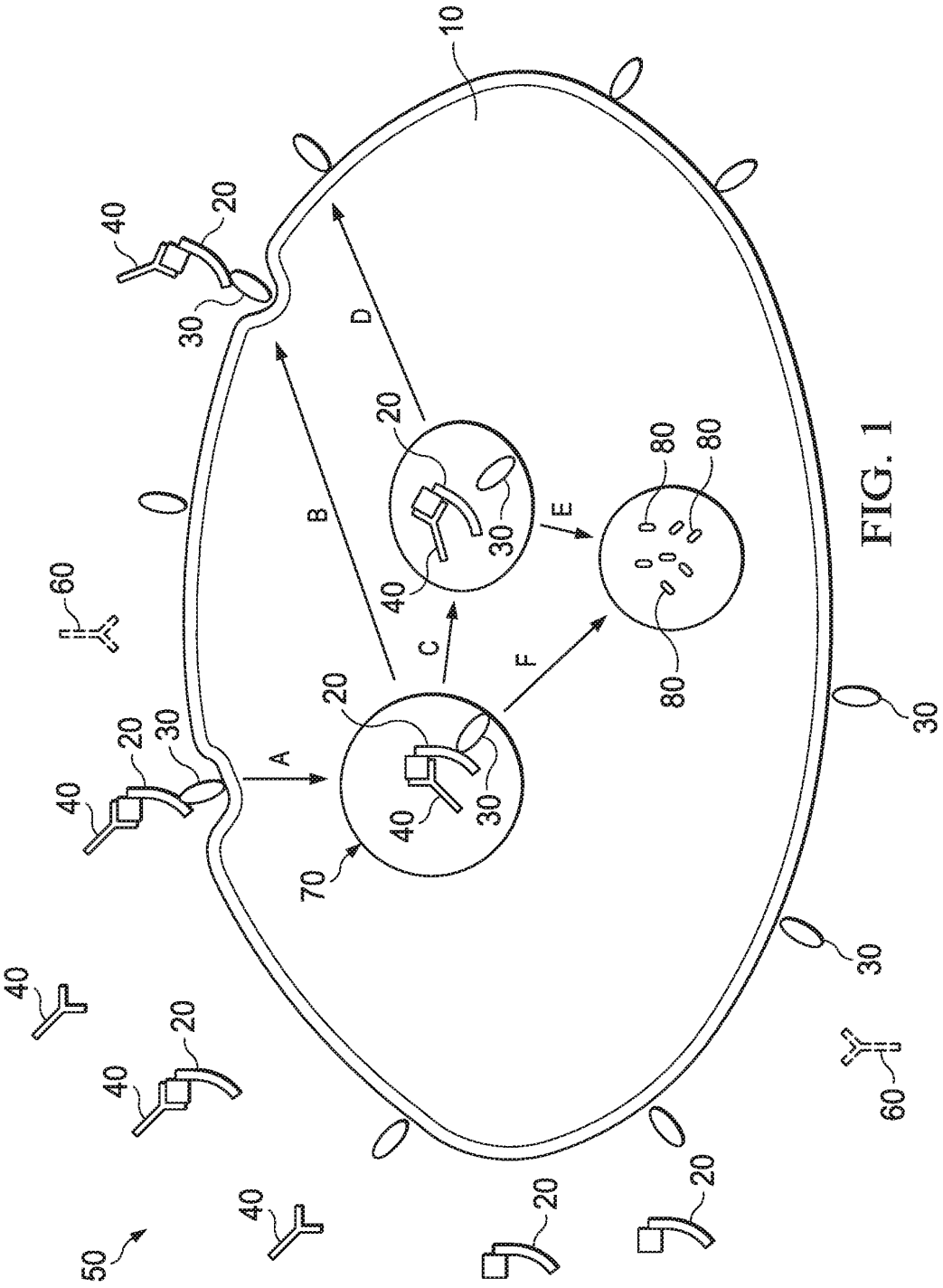


FIG. 1

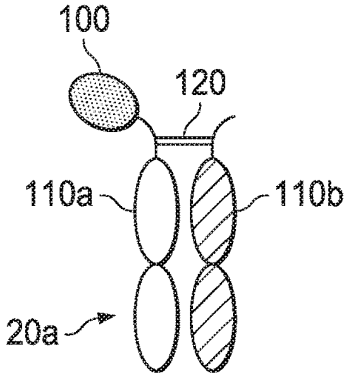


FIG. 2A

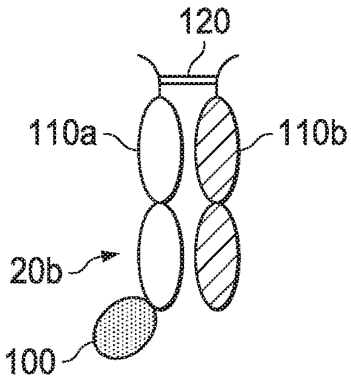


FIG. 2B

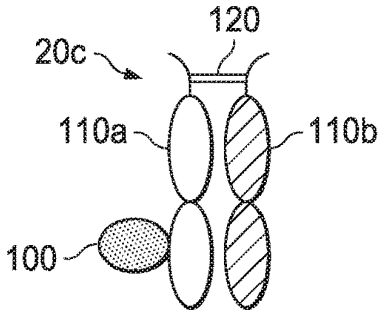


FIG. 2C

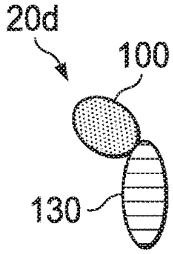


FIG. 2D

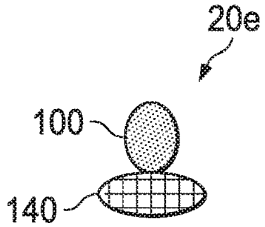


FIG. 2E

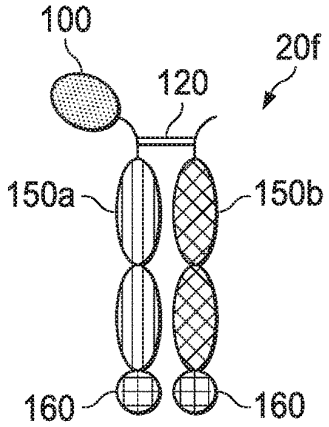


FIG. 2F

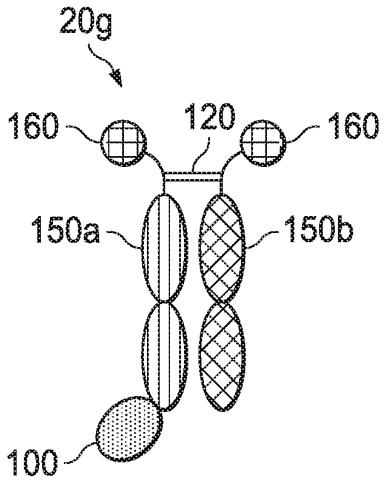


FIG. 2G

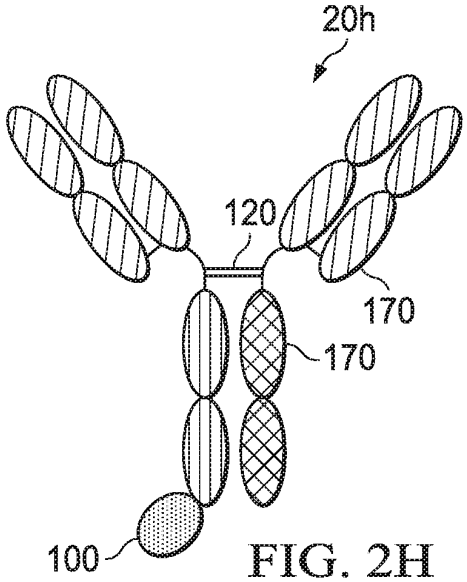


FIG. 2H

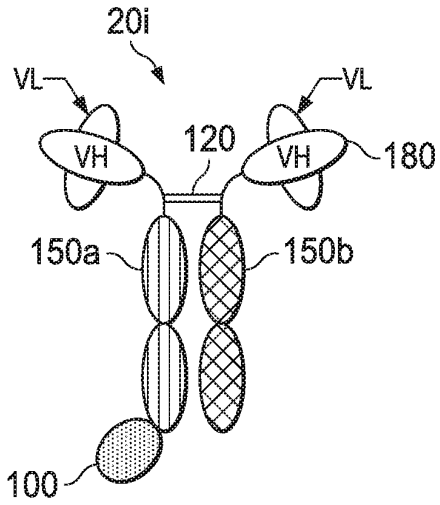


FIG. 2I

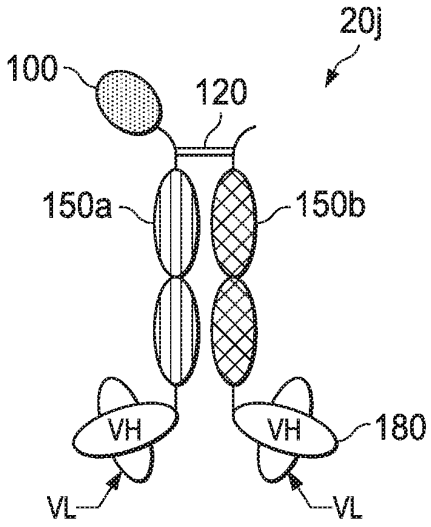


FIG. 2J

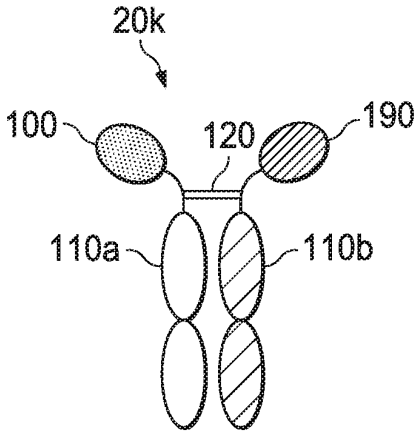


FIG. 2K

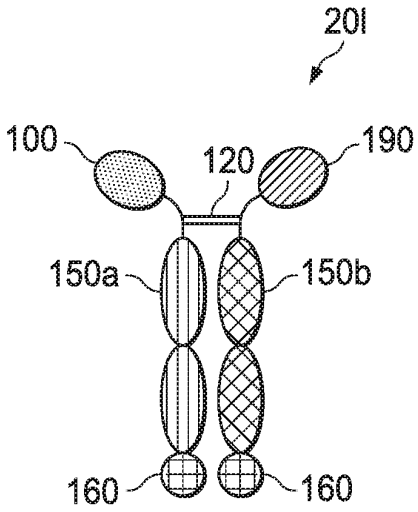


FIG. 2L

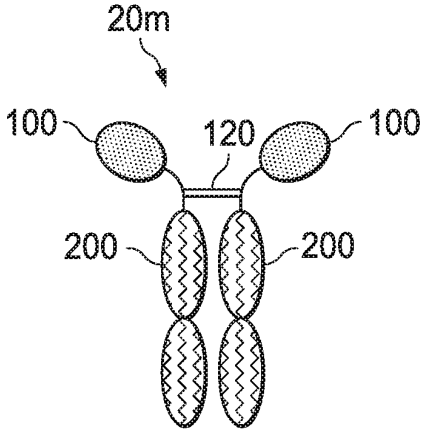


FIG. 2M

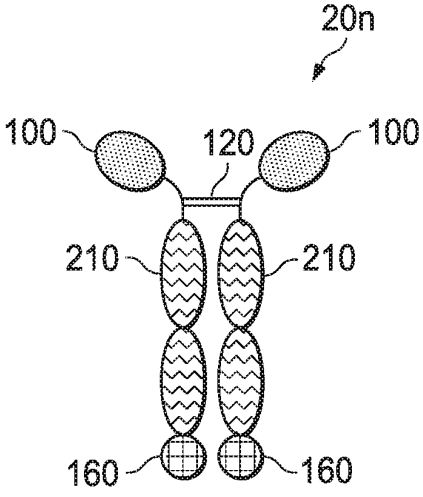


FIG. 2N

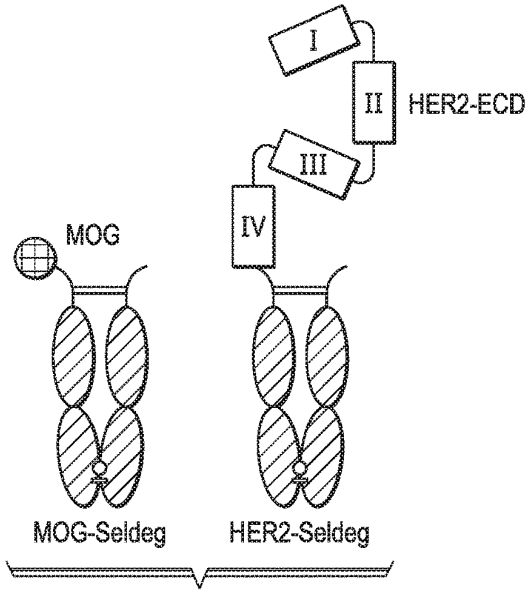

I
II
HER2-ECD
III
IV
MOG
MOG-Seldeg
HER2-Seldeg

FIG. 3A

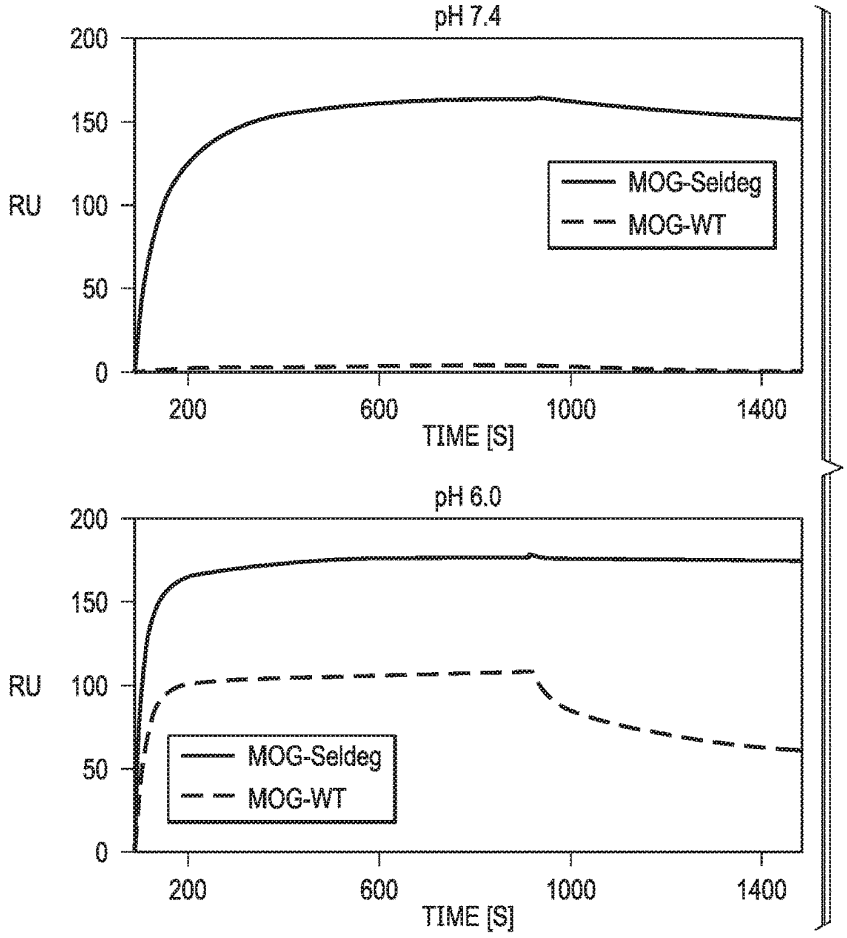

pH 7.4
RU
200
150
100
50
0
MOG-Seldeg
MOG-WT
200
600
1000
1400
TIME [S]
pH 6.0
RU
200
150
100
50
0
MOG-Seldeg
MOG-WT
200
600
1000
1400
TIME [S]

FIG. 3B

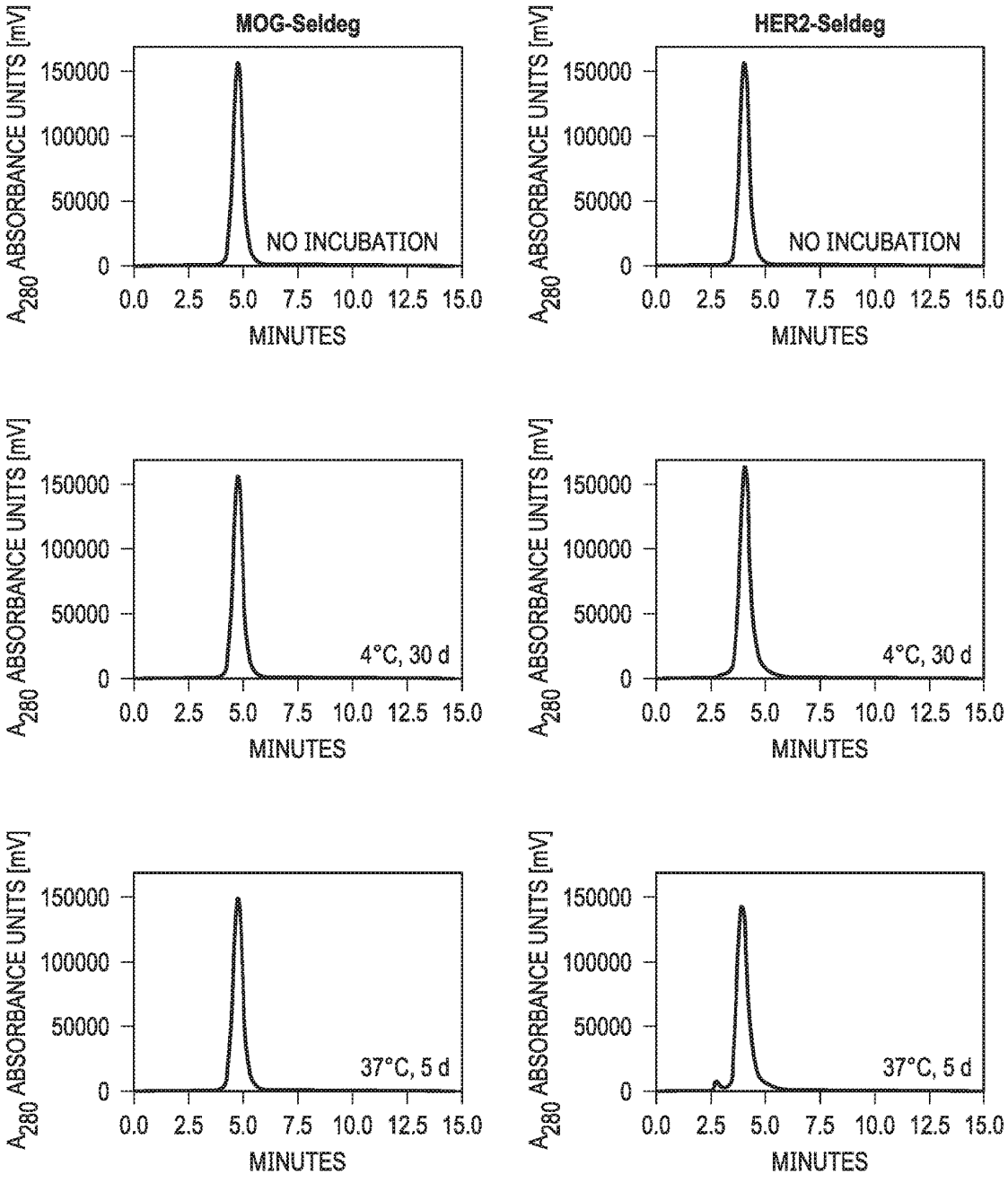

MOG-Seldeg
HER2-Seldeg
NO INCUBATION
4°C, 30 d
37°C, 5 d
A280 ABSORBANCE UNITS [mV]
150000
100000
50000
0
0.0 2.5 5.0 7.5 10.0 12.5 15.0
MINUTES

FIG. 3C

FIG. 3D

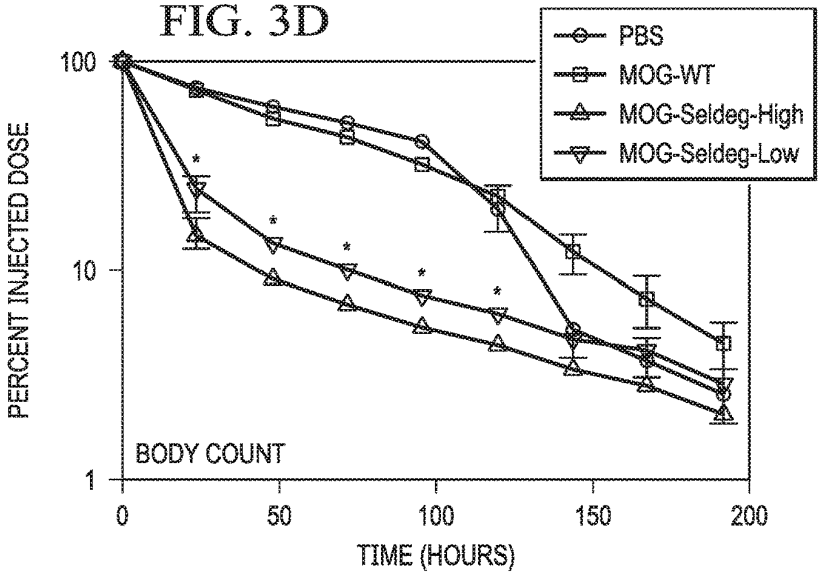

PBS
MOG-WT
MOG-Seldeg-High
MOG-Seldeg-Low
PERCENT INJECTED DOSE
100
10
1
BODY COUNT
0
50
100
150
200
TIME (HOURS)

FIG. 3E

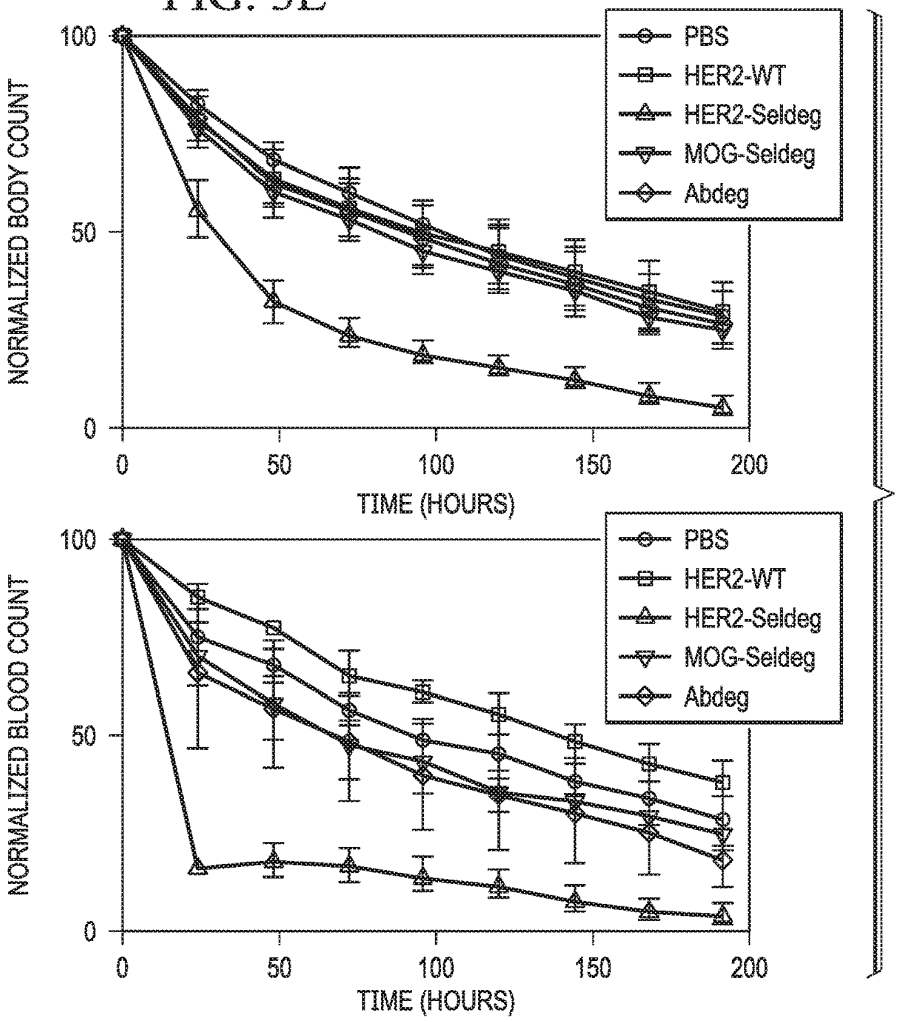
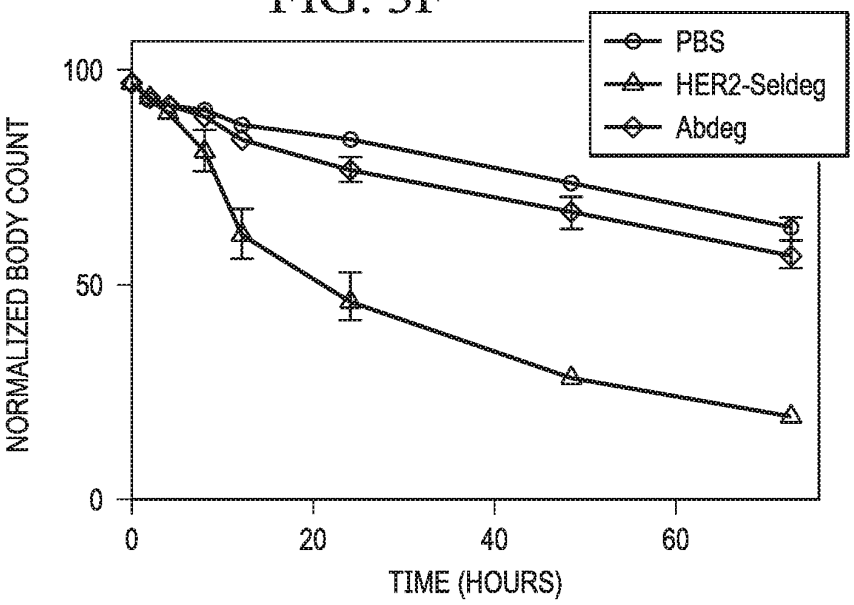

PBS
HER2-WT
HER2-Seldeg
MOG-Seldeg
Abdeg
NORMALIZED BODY COUNT
100
50
0
0
50
100
150
200
TIME (HOURS)
PBS
HER2-WT
HER2-Seldeg
MOG-Seldeg
Abdeg
NORMALIZED BLOOD COUNT
100
50
0
0
50
100
150
200
TIME (HOURS)

FIG. 3F


PBS
HER2-Seldeg
Abdeg
NORMALIZED BODY COUNT
100
50
0
0
20
40
60
TIME (HOURS)

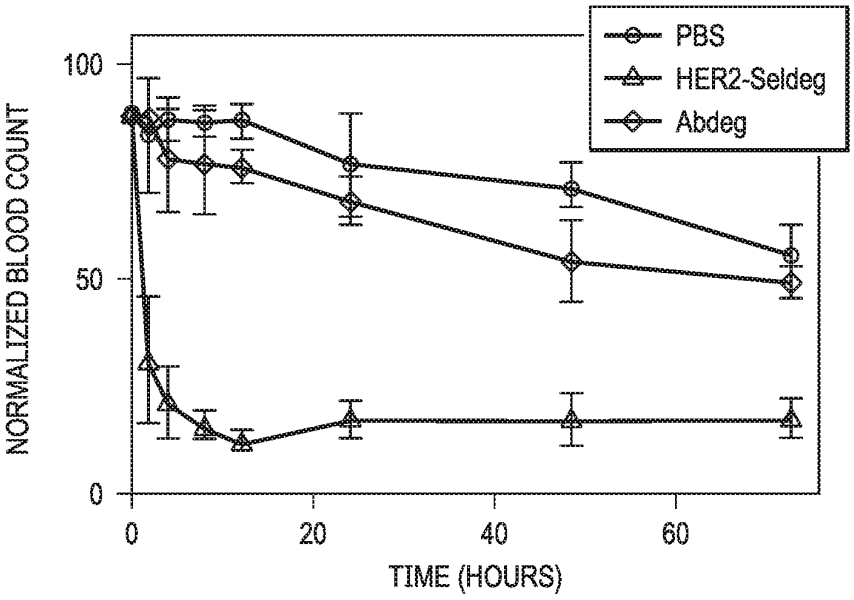

PBS
HER2-Seldeg
Abdeg
NORMALIZED BLOOD COUNT
100
50
0
0
20
40
60
TIME (HOURS)

FIG. 4A

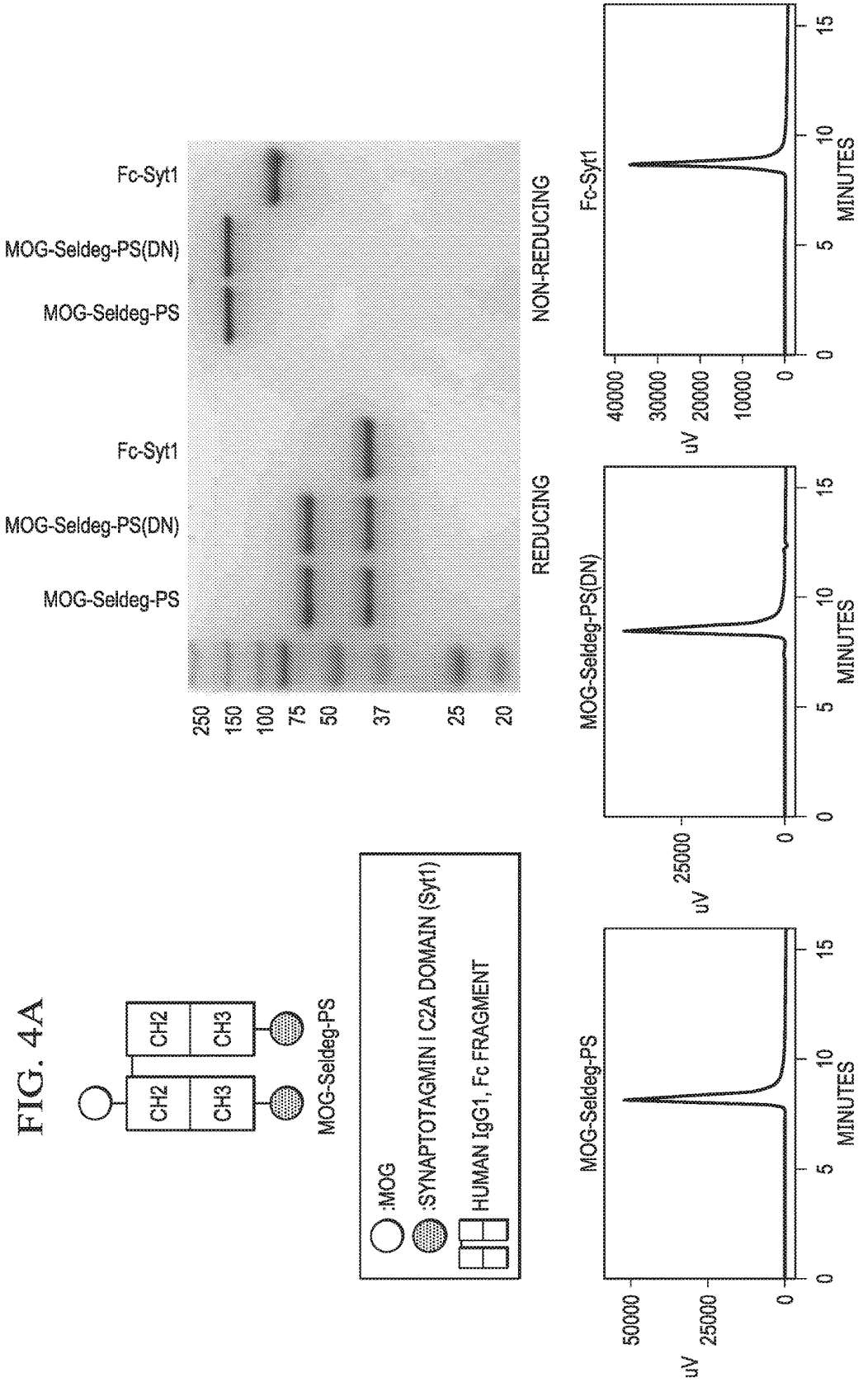
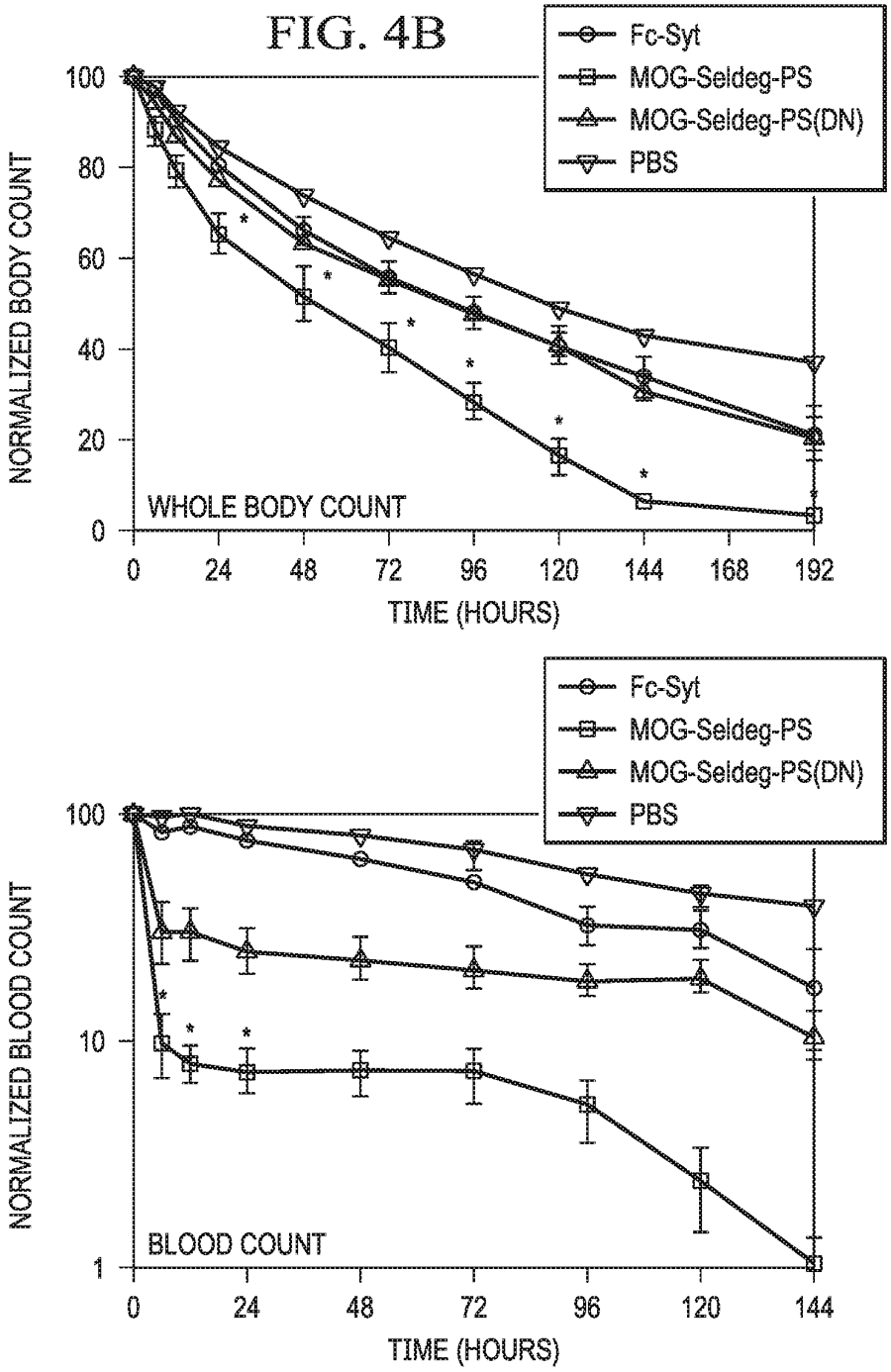

CH2
CH3
CH2
CH3
MOG-Seldeg-PS
:MOG
:SYNAPTOTAGMIN I C2A DOMAIN (Syt1)
HUMAN IgG1, Fc FRAGMENT
Fc-Syt1
MOG-Seldeg-PS(DN)
MOG-Seldeg-PS
Fc-Syt1
MOG-Seldeg-PS(DN)
MOG-Seldeg-PS
250
150
100
75
50
37
25
20
REDUCING
NON-REDUCING
MOG-Seldeg-PS
MOG-Seldeg-PS(DN)
Fc-Syt1
uV
MINUTES

FIG. 4B


Fc-Syt
MOG-Seldeg-PS
MOG-Seldeg-PS(DN)
PBS
NORMALIZED BODY COUNT
100
80
60
40
20
0
WHOLE BODY COUNT
0
24
48
72
96
120
144
168
192
TIME (HOURS)
Fc-Syt
MOG-Seldeg-PS
MOG-Seldeg-PS(DN)
PBS
NORMALIZED BLOOD COUNT
100
10
1
BLOOD COUNT
0
24
48
72
96
120
144
TIME (HOURS)

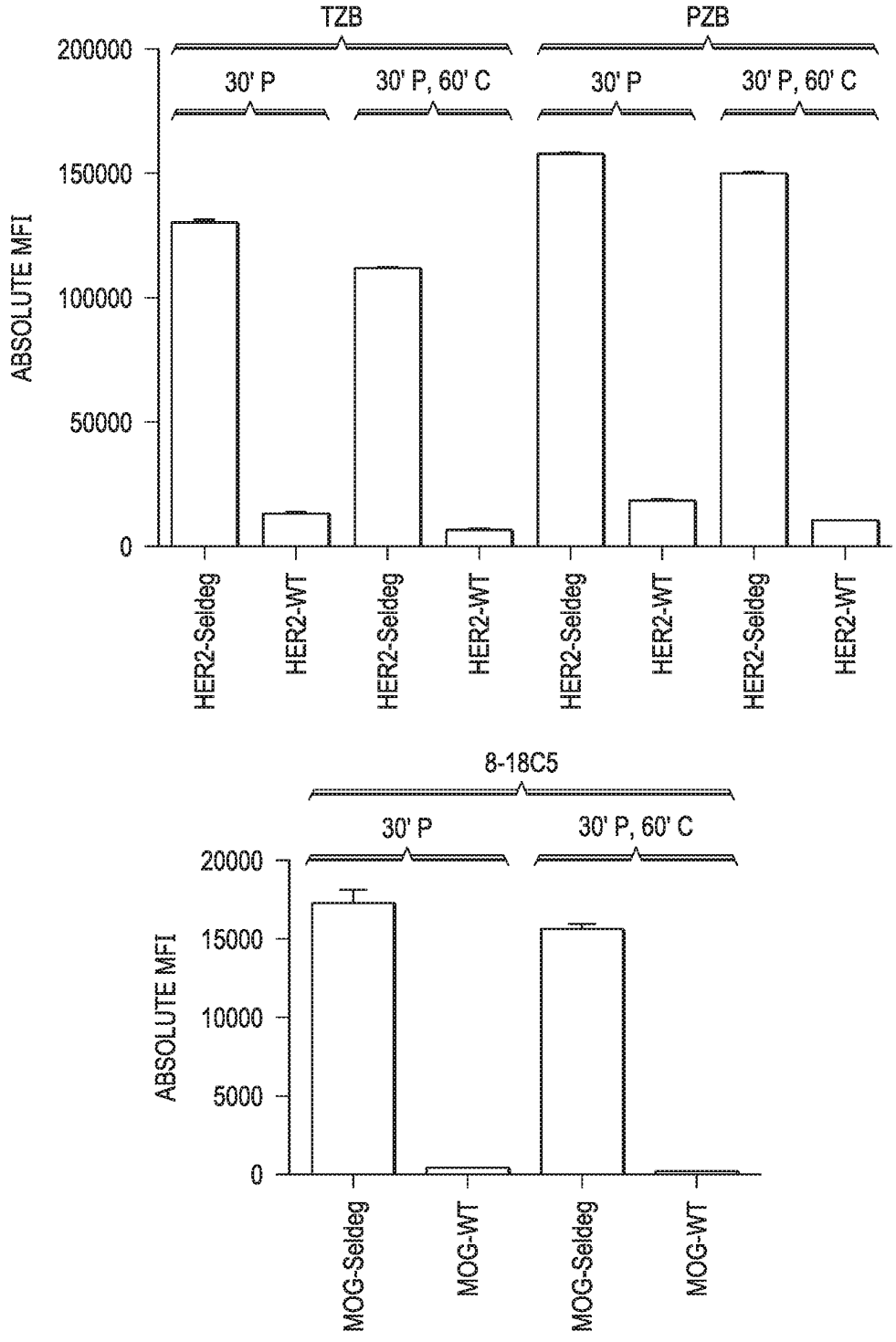

TZB
PZB
30' P
30' P, 60' C
30' P
30' P, 60' C
200000
150000
100000
50000
0
ABSOLUTE MFI
HER2-Seldeg
HER2-WT
HER2-Seldeg
HER2-WT
HER2-Seldeg
HER2-WT
HER2-Seldeg
HER2-WT
8-18C5
30' P
30' P, 60' C
20000
15000
10000
5000
0
ABSOLUTE MFI
MOG-Seldeg
MOG-WT
MOG-Seldeg
MOG-WT

FIG. 5A

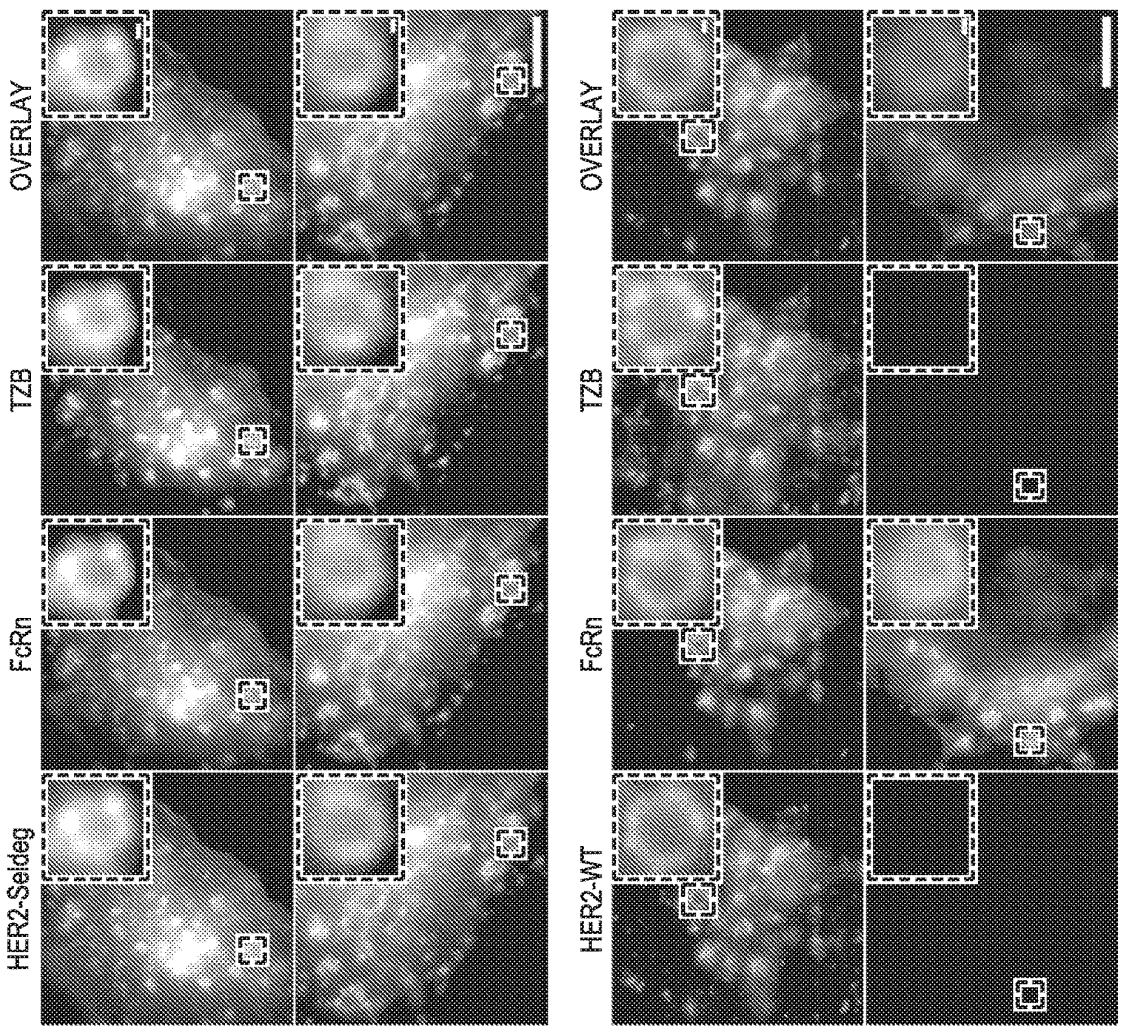

HER2-Seldeg
FcRn
TZB
OVERLAY
30' P
30' P, 60' C
HER2-WT
FcRn
TZB
OVERLAY
30' P
30' P, 60' C

FIG. 5B

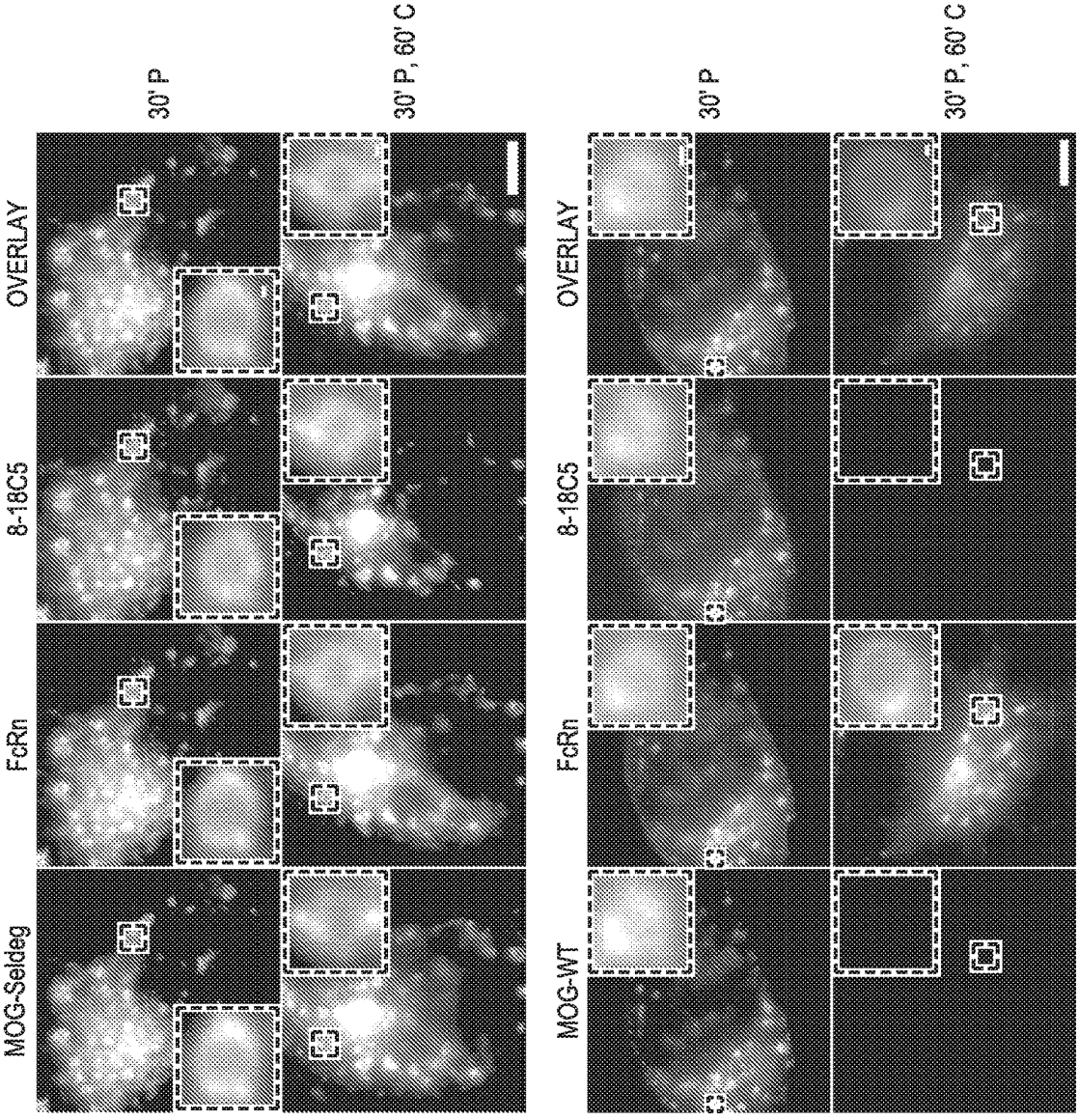

MOG-Seldeg
FcRn
8-18C5
OVERLAY
30' P
30' P, 60' C
MOG-WT
FcRn
8-18C5
OVERLAY
30' P
30' P, 60' C

FIG. 5C

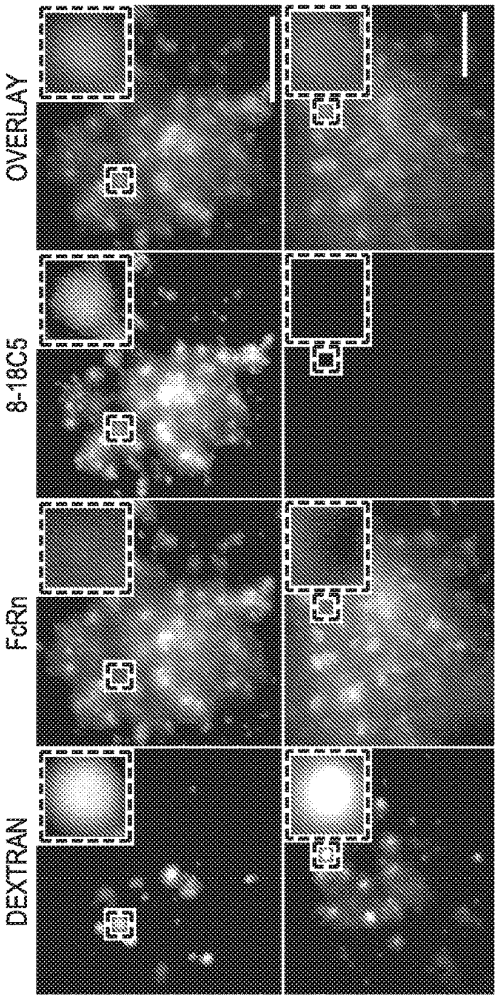

DEXTRAN
FcRn
8-18C5
OVERLAY
MOG-Seldeg
MOG-WT

FIG. 6A

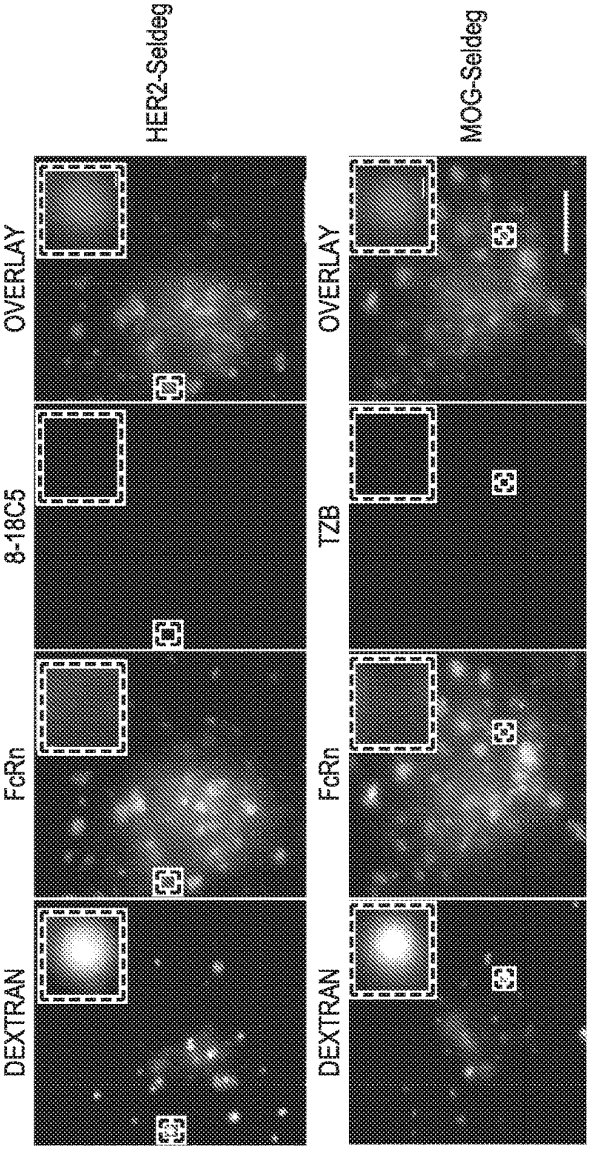

DEXTRAN
FcRn
8-18C5
OVERLAY
HER2-Seldeg
DEXTRAN
FcRn
TZB
OVERLAY
MOG-Seldeg

FIG. 6B

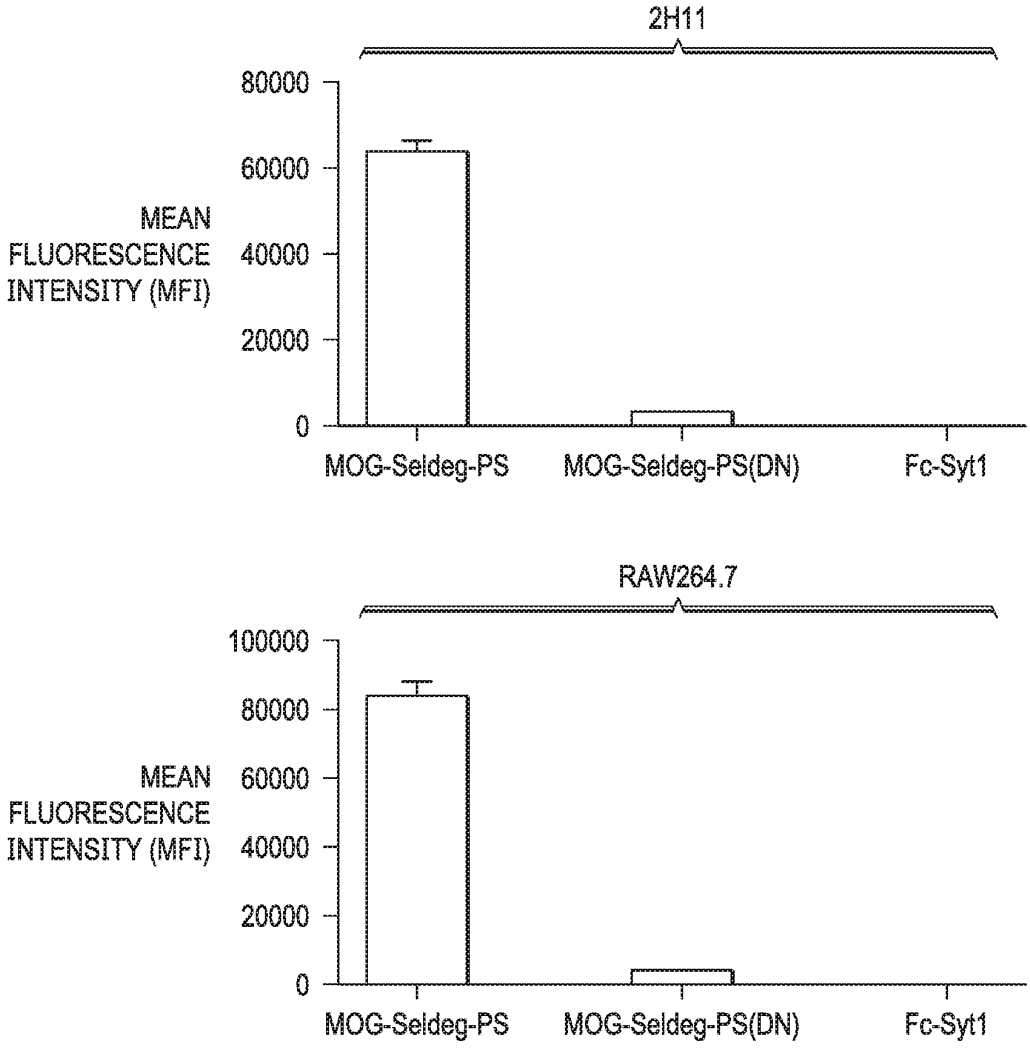
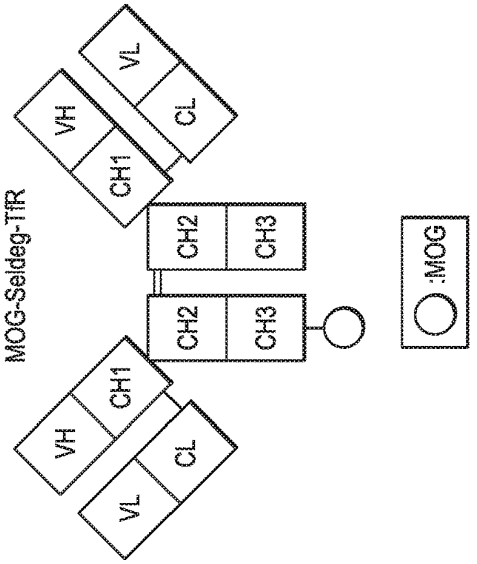
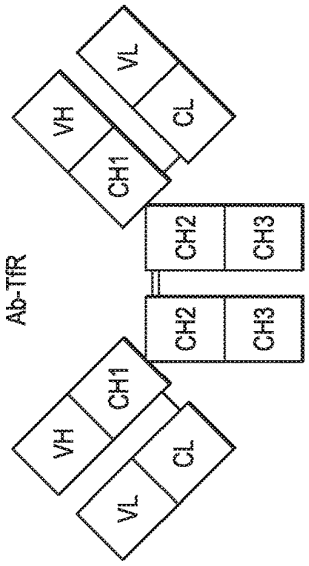
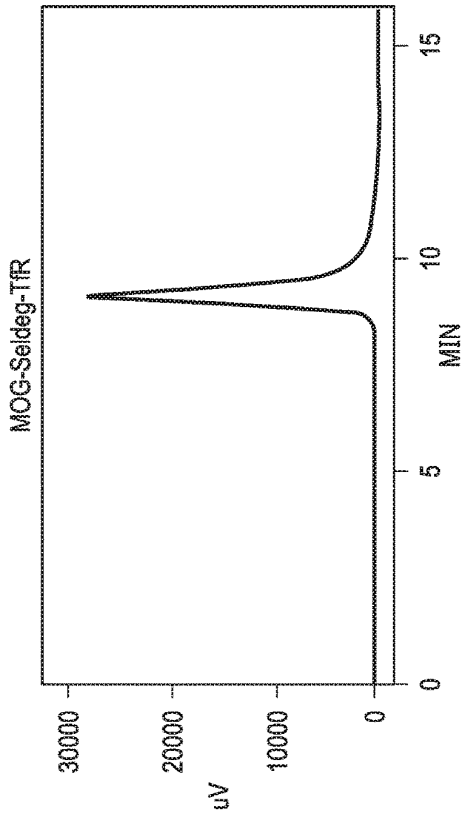

2H11
80000
60000
40000
20000
0
MEAN FLUORESCENCE INTENSITY (MFI)
MOG-Seldeg-PS
MOG-Seldeg-PS(DN)
Fc-Syt1
RAW264.7
100000
80000
60000
40000
20000
0
MEAN FLUORESCENCE INTENSITY (MFI)
MOG-Seldeg-PS
MOG-Seldeg-PS(DN)
Fc-Syt1

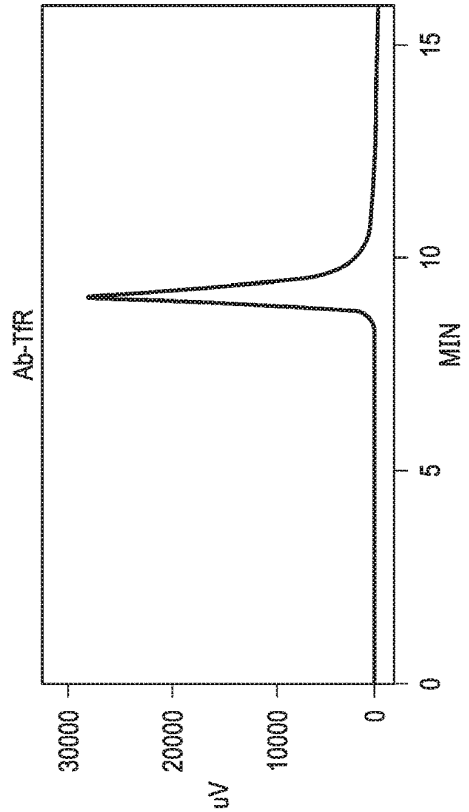
FIG. 7

FIG. 8


MOG-Seldeg-TfR
VH
CH1
VL
CL
CH2
CH3
:MOG


Ab-TfR
VH
CH1
VL
CL
CH2
CH3


MOG-Seldeg-TfR
uV
30000
20000
10000
0
0
5
10
15
MIN


Ab-TfR
uV
30000
20000
10000
0
0
5
10
15
MIN

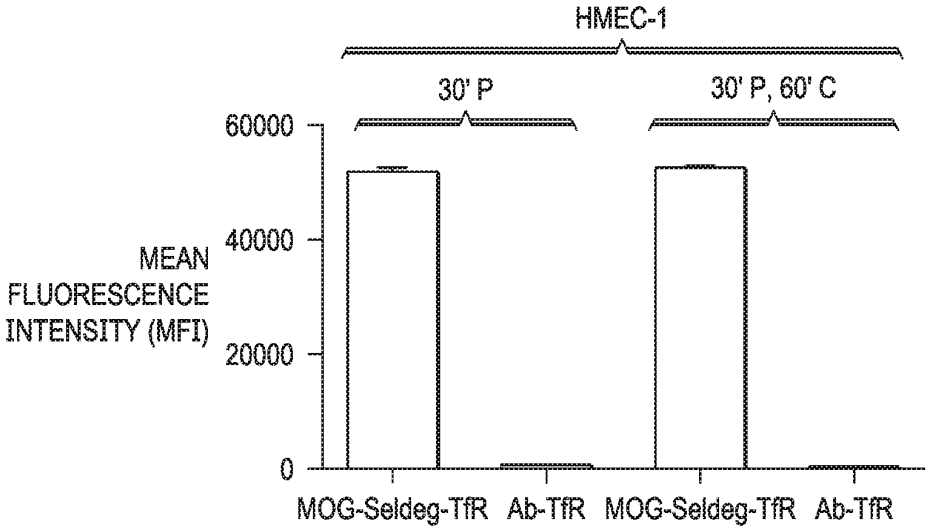

HMEC-1
30' P
30' P, 60' C
60000
40000
20000
0
MEAN FLUORESCENCE INTENSITY (MFI)
MOG-Seldeg-TfR
Ab-TfR
MOG-Seldeg-TfR
Ab-TfR

FIG. 9

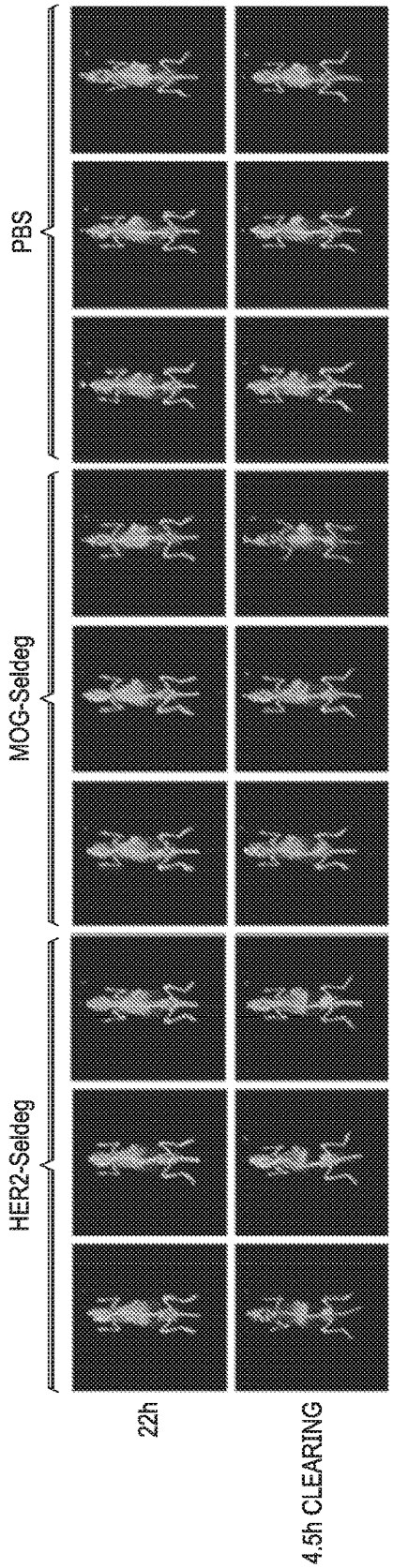


FIG. 10A

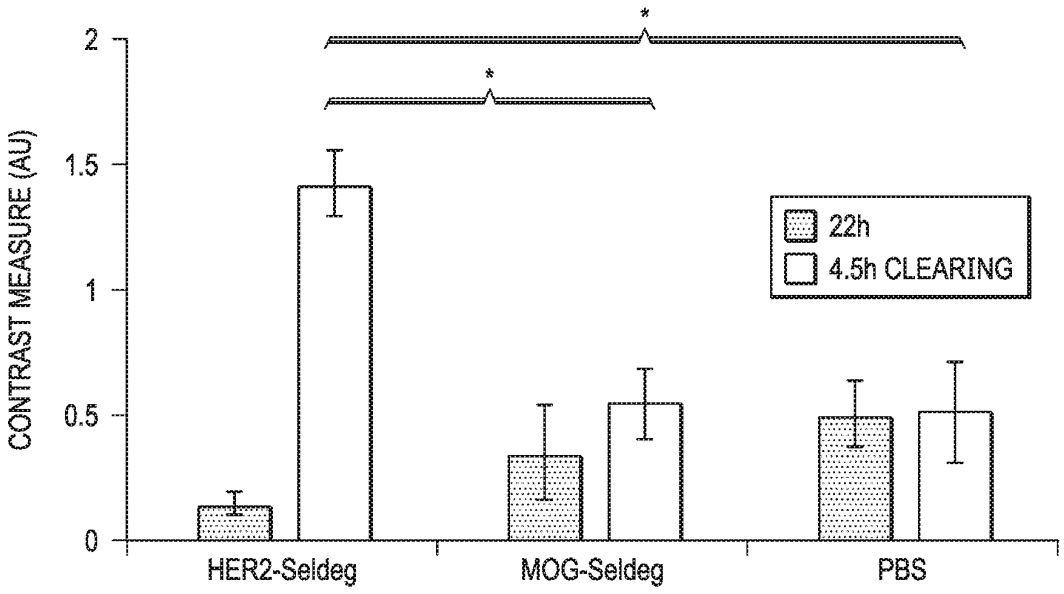

CONTRAST MEASURE (AU)
2
1.5
1
0.5
0
*
*
22h
4.5h CLEARING
HER2-Seldeg
MOG-Seldeg
PBS

FIG. 10B

FUSION PROTEINS (SELDEGS) FOR SELECTIVELY DEPLETING ANTIGEN-SPECIFIC ANTIBODIES AND METHODS OF USE THEREOF

TECHNICAL FIELD

This disclosure relates to engineered proteins, and more specifically, to fusion proteins that selectively deplete target antigen-specific antibodies from the body ("Seldegs").

BACKGROUND

Antibodies are Y-shaped proteins present in blood and other body fluids of the human body and the bodies of mammals. Antibodies are a critical component of the body's immune system. They function by recognizing a unique part of a foreign target, called the antigen. An antibody is able to selectively recognize and trigger an immune response to an antigen through its two antigen-binding sites. Each antigen-binding site is at the end of each upper tip of the antibody's Y-shape. The target antigen may bind one or both antigen-binding sites. The base of an antibody's Y-shape is called an Fc fragment. When an antibody binds to its target, the Fc region can bring about target clearance through antibody effector functions. Such responses can include cellular processes to destroy the antigen. In certain autoimmune diseases and other illnesses, pathogenic antibodies may be created that target self-antigens in the body, contributing to pathogenesis. An antibody may be in either of two physical forms, a soluble form that is secreted from the cell and is free in the blood plasma, or a membrane-bound form that is attached to the outer-membrane of a B cell. The secreted antibodies cause pathology in diseases involving autoreactive antibodies. They can also contribute to transplant rejection or the elimination of protein-based therapeutics.

Due to their ability to bind specifically to target molecules, antibodies can be used to treat diseases such as cancer and autoimmunity. They also have applications in the detection of tumors during whole body imaging using, for example, radiolabeled antibodies in positron emission tomography (PET). However, their relatively long in vivo persistence can lead to high background in non-tumor tissue, resulting in poor contrast for tumor imaging and undesirable off-target effects.

SUMMARY

The present disclosure includes fusion proteins, herein referred to as "Seldegs", that are configured to allow selective clearance of antigen-specific antibodies. A Seldeg includes a targeting component that is configured to specifically bind to a cell surface receptor or other cell surface molecule, and an antigen component that is configured to specifically bind to an antigen-specific antibody or a variant thereof.

The targeting component of the Seldeg includes a protein or a protein fragment that is configured to specifically bind to a cell surface receptor or other cell surface molecule. The antigen component of the Seldeg includes one molecule of an antigen or antigen fragment or antigen mimetic configured to specifically bind a target antigen-specific antibody. The antigen component is fused directly or indirectly to the targeting component.

The present disclosure also includes a method of depleting a target antigen-specific antibody from a patient by administering to the patient a Seldeg in an amount sufficient to remove at least 50% of the target antigen-specific antibody from the circulation or a target tissue in the patient.

The above Seldegs and methods may further include the following details, which may be combined with one another unless clearly mutually exclusive: i) the targeting component can bind to the cell surface receptor or cell surface molecule with a dissociation constant of less than 10 μM at near-neutral pH, ii) near-neutral pH may be greater than 6.8 and less than 7.5; iii) the Seldeg can comprise at least a first targeting component and a second targeting component, wherein the protein or protein fragment of the first targeting component is configured to bind to a different cell surface receptor or a different cell surface molecule than the protein or protein fragment of the second targeting component; iv) the targeting component may include a heterodimer of two immunoglobulin Fc fragments in which one immunoglobulin Fc fragment of the heterodimer is fused to the antigen component and the other immunoglobulin Fc fragment may not be; v) the immunoglobulin Fc fragment may have substantially reduced binding or no detectable binding to Fc gamma receptors; vi) the immunoglobulin Fc fragments can be derived from an immunoglobulin class or isotype that does not bind to Fc gamma receptors or complement; vii) the immunoglobulin Fc fragments can be configured to bind to Fc gamma receptors and complement; viii) at least one of the immunoglobulin Fc fragments can be modified to have a higher binding affinity for FcRn at near-neutral pH than an unmodified immunoglobulin Fc fragment; ix) the antigen component may be fused to one immunoglobulin Fc fragment at an N-terminus or a C-terminus of a hinge-CH_2—CH domain of the immunoglobulin Fc fragment; x) the immunoglobulin Fc fragments may be modified to have no binding affinity for Fc gamma receptors and/or complement (C1q), or lower binding affinity for Fc gamma receptors and/or complement (C1q) than unmodified immunoglobulin Fc fragments; xi) the targeting component may include one or more antibody variable regions or fragments thereof that are configured to specifically bind to the cell surface receptor or the cell surface molecule; xii) the antibody variable region or fragment thereof may include at least one nanobody, xiii) the nanobody may be a nanobody multimer in which one nanobody is fused to the antigen component and all other nanobodies in the nanobody multimer may not be; xiv) the targeting component may be configured to dissociate from the cell surface receptor or cell surface molecule following entry into an endosome of a complex comprising the Seldeg and the cell surface receptor or cell surface molecule; xv) the antigen component may be fused to an N-terminal location or a C-terminal location on the targeting component; xvi) the antigen component may be fused to a non-terminal location on the targeting component; xvii) the antigen component may be fused to the targeting component via a chemical reaction, through a linker, or during formation of a single combined antigen component-targeting component fusion protein; xviii) the targeting component can be one or more albumin molecules, albumin fragments or mutated albumin variants that are configured to specifically bind to a FcRn; xix) the targeting component can include one or more antibody variable domains or nanobodies that are configured to bind to a transferrin receptor; xx) the targeting component can include one or more protein molecules or protein domains configured to bind to a transferrin receptor; xxi) the targeting component can include one or more protein molecules or protein domains configured to bind to a phosphatidylserine; xxii) the targeting protein component can include one or more antibody variable domains or nanobodies configured to bind to a phosphati-

dylserine; xxiii) the one or more protein molecules or protein domains can be configured to bind the phosphatidylserine via a calcium-dependent mechanism; xxiv) the targeting component can include a C2A domain of synaptotagmin 1; xxv) the Seldeg can include at least a first antigen component and a second antigen component, wherein the one molecule of the antigen, antigen fragment or antigen mimetic of the first antigen component is different to the one molecule of the antigen molecule, antigen fragment or antigen mimetic of the second antigen component; xxvi) the Seldeg can include at least a first antigen component and a second antigen component, wherein the one molecule of the antigen, antigen fragment or antigen mimetic of the first antigen component is the same as the one molecule of the antigen molecule, antigen fragment or antigen mimetic of the second antigen component; xxvii) the method may include administering an amount sufficient of Seldeg to remove at least 50% of the target antigen-specific antibody from the circulation or the target tissue in the patient within five hours of administration; xxviii) the method may include administering a Seldeg having a targeting component that includes a protein or protein fragment configured to bind to the cell surface receptor or other cell surface molecule with a dissociation constant of less than 10 μM at near neutral pH; xxix) the amount sufficient of Seldeg administered may be an amount at least equimolar to the amount of target antigen-specific antibody to be depleted, xxx) the method may include administering the Seldeg in an amount sufficient to remove at least 90% of the target antigen-specific antibody from the circulation or target tissue in the patient within two hours of administration; xxxi) the Seldeg may be administered in an amount sufficient to remove at least 50% of the target antigen-specific antibody from the circulation or target tissue in the patient within one hour of administration; xxxii) the Seldeg may be re-administered whenever 50% of patients are expected to have regenerated a threshold amount of target antigen-specific antibody in the circulation or target tissue; xxxiii) the Seldeg may remove less than 10% of non-target antibodies in the circulation or in the tissue targeted by the target antigen-specific antibody; xxxiv) the Seldeg may remove an amount of non-targeted antibodies in the circulation or in the target tissue of the patient that does not cause a clinically adverse effect in the patient; xxxv) the Seldeg may remove less than 1% of non-target antibodies in the circulation or in a tissue targeted by the target antigen-specific antibody; xxxvi) the Seldeg may cause degradation of the target antigen-specific antibody by a cell expressing the cell surface receptor or cell surface molecule; xxxvii) the Seldeg may be administered to a patient with an autoimmune disease and the target antigen-specific antibody may specifically bind to an autoantigen; xxxviii) the Seldeg may be administered to a patient receiving a transplanted organ and the target antigen-specific antibody may specifically bind to an antigen on the transplanted organ; xxxix) the Seldeg may be administered to increase contrast during tumor imaging and the target antigen-specific antibody may specifically bind to a tumor antigen; xl) the Seldeg may be administered to a patient who has received a biologic and the target antigen-specific antibody may be the biologic; xli) the Seldeg may be administered to a patient prior to the delivery of a therapeutic agent, if the patient has antibodies specific for the therapeutic agent, and the Seldeg is configured to target the antibodies specific for the therapeutic agent; xlii) the Seldeg may be administered to provide a PET image contrast agent; xliii) the target antigen-specific antibody may be an anti-MOO antibody; xliv) the target antigen-specific antibody may be an anti-HER2 antibody; xlv) the Seldeg may include proteins having amino acid sequences of at least one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, or SEQ ID NO: 34, or a homolog thereof; xlvi) the Seldeg may include a heterodimer of proteins having amino acid sequences of SEQ ID NO: 2 plus SEQ ID NO: 6, SEQ ID NO: 4 plus SEQ ID NO: 6, SEQ ID NO: 8 plus SEQ ID NO: 10, SEQ ID NO: 12 plus SEQ ID NO: 14, SEQ ID NO: 16 plus SEQ ID NO: 18 plus SEQ ID NO: 20, SEQ ID NO: 20 plus SEQ ID NO: 22 plus SEQ ID NO: 24, SEQ ID NO: 26 plus SEQ ID NO: 28, SEQ ID NO: 30 plus SEQ ID NO: 6, SEQ ID NO: 32 plus SEQ ID NO: 6, or SEQ ID NO: 34 plus SEQ ID NO: 6, or homologs thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

For a more complete understanding of the present invention and its features and advantages, reference is now made to the following description, taken in conjunction with the accompanying drawings, which are not to scale, in which like numerals refer to like features, and in which:

FIG. **1** is a schematic diagram of selected cellular events that lead to the degradation of antigen-specific antibodies in the presence of Seldegs;

FIG. **2**A is a schematic diagram of a Seldeg including an antigen fused to a N-terminal location of an Fc fragment,

FIG. **2**B is a schematic diagram of a Seldeg including an antigen fused to a C-terminal location of an Fc fragment;

FIG. **2**C is a schematic diagram of a Seldeg including an antigen fused to a non-terminal location of an Fc fragment;

FIG. **2**D is a schematic diagram of a Seldeg including an antigen fused to a terminal location of a protein or protein fragment that binds to a cell surface receptor or cell surface molecule;

FIG. **2**E is a schematic diagram of a Seldeg including an antigen fused to a non-terminal location of a protein or protein fragment that binds to a cell surface receptor or cell surface molecule;

FIG. **2**F is a schematic diagram of a Seldeg including an antigen fused to a N-terminal location of an Fc fragment and protein or protein fragments that bind to a cell surface protein or cell surface receptor fused to the C-termini of the Fc fragment;

FIG. **2**G is a schematic diagram of a Seldeg including an antigen fused to a C-terminal location of an Fc fragment and protein or protein fragments that bind to a cell surface protein or cell surface receptor fused to the N-termini of the Fc fragment,

FIG. **2**H is a schematic diagram of a Seldeg including an antigen fused to a C-terminal location of an antibody that binds to a cell surface protein or cell surface receptor,

FIG. **2**I is a schematic diagram of a Seldeg including an antigen fused to a C-terminal location of an Fc fragment and scFv fragments that bind to a cell surface protein or cell surface receptor fused to the N-termini of the Fc fragment.

FIG. **2**J is a schematic diagram of a Seldeg including an antigen fused to a N-terminal location of an Fc fragment and scFv fragments that bind to a cell surface protein or cell surface receptor fused to the C-termini of the Fc fragment;

FIG. **2**K is a schematic diagram of a Seldeg including two different antigens fused to the N-terminal locations of an Fc fragment;

FIG. **2**L is a schematic diagram of a Seldeg comprising two different antigens fused to the N-terminal locations of an Fc fragment and protein or protein fragments that bind to a cell surface protein or cell surface receptor fused to the C-termini of the Fc fragment;

FIG. **2**M is a schematic diagram of a Seldeg comprising two antigen molecules fused to the N-terminal locations of an Fc fragment;

FIG. **2**N is a schematic diagram of a Seldeg comprising two antigen molecules fused to the N-terminal locations of an Fc fragment and protein or protein fragments that bind to a cell surface protein or cell surface receptor fused to the C-termini of the Fc fragment;

FIG. **3**A is a schematic diagram of two exemplary FcRn-targeting Seldegs, a human epidermal growth factor receptor 2 Seldeg ("HER2-Seldeg") and a myelin oligodendrocyte glycoprotein Seldeg ("MOG-Seldeg");

FIG. **3**B shows the increased binding of an exemplary FcRn-targeting Seldeg to FcRn at pH 6.0 and 7.4.

FIG. **3**C shows HPLC analyses of two exemplary FcRn-targeting Seldegs following incubation at 4° C. (30 days) and 37° C. (5 days) to evaluate their storage stability.

FIG. **3**D shows a graph reporting exemplary normalized body counts versus time, showing clearance of an antigen-specific antibody by an exemplary FcRn-targeting Seldeg;

FIG. **3**E shows additional graphs reporting exemplary normalized blood and body count versus time, showing clearance of an antigen-specific antibody by an exemplary FcRn-targeting Seldeg;

FIG. **3**F shows additional graphs reporting exemplary normalized blood and body count versus time, showing clearance of an antigen-specific antibody by an exemplary FcRn-targeting Seldeg;

FIG. **4**A shows in the upper left panel a schematic diagram of an exemplary Seldeg referred to as MOG-Seldeg-PS comprising an antigen fused to targeting protein (C2A domain of synaptotagmin 1, Syt1) that binds to phosphatidylserine (PS); in the upper right panel FIG. **4**A shows exemplary SDS-PAGE gels (reducing and non-reducing conditions) of recombinant proteins of MOG-Seldeg-PS, MOG-Seldeg-PS(DN) with mutations that substantially reduce binding to PS, and Fc-Syt1 that has no antigen (MOG) attached; in the lower panel, FIG. **4**A shows exemplary HPLC profiles of the recombinant proteins that are shown in the upper right FIG. **4**A, MOG-Seldeg-PS, MOG-Seldeg-PS(DN) and Fc-Syt1;

FIG. **4**B shows additional graphs reporting exemplary normalized blood and body count versus time, showing clearance of an antigen-specific antibody by an exemplary PS-targeting Seldeg;

FIG. **5**A shows graphs reporting exemplary data showing the accumulation of antigen-specific antibodies in cells in the presence of exemplary FcRn-targeting Seldegs and control proteins;

FIG. **5**B is an exemplary series of microscopic images of an exemplary FcRn-targeting Seldeg and control protein in the presence of target antigen-specific antibodies, with microscopic images of representative endosomes cropped, expanded, and presented in the top right-corner insets;

FIG. **5**C is another series of exemplary microscopic images of an exemplary FcRn-targeting Seldeg and control protein in the presence of target antigen-specific antibodies, with microscopic images of representative endosomes cropped, expanded, and presented in the top right-corner insets;

FIG. **6**A is another series of exemplary microscopic images of an exemplary FcRn-targeting Seldeg and control protein in the presence of target antigen-specific antibodies, with microscopic images of representative lysosomes cropped, expanded, and presented in the top right-corner insets;

FIG. **6**B is another series of exemplary microscopic images of exemplary FcRn-targeting Seldegs in the presence of antigen-specific antibodies that do not recognize the antigen that is being targeted by the Seldeg, with microscopic images of representative lysosomes cropped, expanded, and presented in the top right-corner insets;

FIG. **7** shows graphs reporting exemplary data showing the accumulation of antigen-specific antibodies in cells in the presence of exemplary PS-targeting Seldegs and control proteins;

FIG. **8** is a schematic diagram of an exemplary Seldeg including an antigen fused to targeting protein (antibody) that binds to the transferrin receptor (TfR), HPLC profiles of the recombinant proteins are shown, including an analysis of the targeting protein (antibody) without antigen (MOG) attached;

FIG. **9** is a graph reporting exemplary data showing the accumulation of antigen-specific antibodies in cells in the presence of an exemplary TfR-targeting Seldeg and control protein;

FIG. **10**A is an exemplary series of positron emission tomography (PET) analyses of tumors in mice following delivery of radiolabeled HER2-specific antibody and treatment with an exemplary FcRn-targeting Seldeg, control protein or vehicle control.

FIG. **10**B shows a graph reporting contrast measures for tumor:thoracic regions of tumor-bearing mice following delivery of radiolabeled HER2-specific antibody and treatment with an exemplary FcRn-targeting Seldeg, control protein or vehicle control.

DETAILED DESCRIPTION

This disclosure relates to engineered proteins, and more specifically, to Seldegs, which are fusion proteins that are configured to selectively target antigen-specific antibodies for depletion from the body. Seldegs cause the selective degradation of the targeted antigen-specific antibodies by binding to the antigen-specific antibodies and directing them to late endosomes or lysosomes, which contain degradative enzymes. A Seldeg is a fusion protein or molecule that includes at least a targeting component and an antigen component. The targeting component includes a protein or protein fragment or other molecule that is configured to bind to a cell surface receptor or other cell surface molecule. The antigen component includes one molecule of an antigen, antigen fragment or antigen mimetic that is recognized by the targeted antigen-specific antibody.

Upon binding of the antigen-specific antibody to the antigen component, a complex is formed comprising the Seldeg and the antigen-specific antibody. The complex is also configured to bind to the cell surface receptor or other cell surface molecule, allowing cellular internalization of a complex that includes the Seldeg, the antigen-specific antibody, and the targeted cell surface receptor or other cell surface molecule (see FIG. **1**). The targeted cell surface receptor or cell surface molecule may dissociate from the complex upon entry into the endosomes, due to acidic pH, low calcium concentrations and/or other conditions that distinguish the endosomal environment from the extracellular environment. Internalization into endosomes and lysosomal entry results in the selective degradation of the complex.

The term "antigen-specific antibody" as used herein refers to an antibody or antibody that binds to a particular antigen, antigen fragment or antigen mimetic.

The term "antigen fragment" as used herein refers to a part of the antigen that can be recognized by the antigen-specific antibody.

The term "antigen mimetic" as used herein refers to a protein, protein fragment, peptide or other molecule that has the same overall shape and properties as the part of the antigen that is recognized by an antigen-specific antibody.

The term "cell surface molecule" as used herein refers to a protein or other biological molecule (e.g. phospholipid, carbohydrate) that is exposed on the plasma membrane of a cell.

Seldegs may include an antigen fused to an Fc fragment of an IgG antibody (herein also referred to as "immunoglobulin Fc fragment"), an FcRn-specific nanobody-antigen fusion molecule, an FcRn-specific antibody that binds to FcRn through its variable region fused to an antigen, an albumin-antigen fusion protein, a PS-binding protein, a TfR-specific antibody or other protein, protein fragment or other molecule that is configured to bind to a cell surface receptor or other cell surface molecule identifiable by skilled persons upon reading of the present disclosure.

Examples of Seldegs described herein include targeting components that are configured to bind to cell surface molecules such as human FcRn, exposed phosphatidylserine (PS) or the transferrin receptor (TfR) with affinities (dissociation constants) of less than 10 μM at near neutral pH.

FcRn and TfR are proteins, and PS is a phospholipid, that may be found on the surface and within multiple different cell types within the body. This invention is not limited to targeting these receptors or cell surface molecules, and many other targets could be envisaged such as the low density lipoprotein receptor, high density lipoprotein receptor, asialoglycoprotein receptor, inhibitory Fc gamma receptors, T cell receptor, B cell receptor, G-protein coupled receptors, insulin receptor, glucagon receptors, galactose receptors, mannose receptors, VEGF receptors, mannose receptors among others identifiable by those skilled in the art. Other targets can be identified in, for example, the following publications or databases. Cell surface receptor protein atlas (Bausch-Fluck, D., Hofmann, A., Bock, T., Frei, A. P., Cerciello, F., Jacobs, A., Moest, H., Omasits, U., Gundry, R. L., Yoon, C., Schiess, R., Schmidt, A., Mirkowska, P., Härtlova, A., Van Eyk, J. E., Bourquin, J P., Aebersold, R., Boheler, K. R., Zandstra, P., Wollscheid, B. (2015) A mass spectrometric-derived cell surface protein atlas. PLoS One 10: e0121314), and the Human protein atlas (https://www.proteinatlas.org/humanproteome/secretome).

The targeting component can bind the cell surface receptor or other cell surface molecule with an affinity (dissociation constant) of less than 10 μM at near-neutral pH.

Accordingly, the targeting component of a Seldeg can include any type of molecule that is configured to specifically bind to a cell surface receptor or other cell surface molecule. Such molecules can include proteins, protein fragments, polynucleotides such as ribonucleic acids or deoxyribonucleic acids, polypeptides, polysaccharides, lipids, amino acids, peptide, sugars and/or other small or large molecules and/or polymers identifiable by skilled persons upon reading of the present disclosure. For example, the targeting component of a Seldeg can include a polynucleotide that is a ligand for a cellular receptor.

The Seldeg can comprise at least a first targeting component and a second targeting component, wherein the protein or protein fragment of the first targeting component is configured to bind to a different cell surface receptor or a different cell surface molecule than the protein or protein fragment of the second targeting component.

As shown in FIG. **1**, a Seldeg **20** may reversibly bind to cell surface receptor or other molecule **30** on the surface of a cell **10**. A target antigen-specific antibody 40, present in extracellular space **50**, may reversibly bind to Seldeg **20**. This binding typically occurs at near-neutral pH, such as at a pH greater than 6.8 and less than 7.5, because that is the typical pH of extracellular space **50**. Non-target antibodies **60** do not bind to Seldeg **20**, or bind with such low affinities that any binding is non-specific. Cell surface receptor or molecule **30** with attached Seldeg **20** and target antigen-specific antibody 40 are internalized into the cell **10** through receptor-mediated uptake into endosome **70** via pathway A. The receptor or other molecule can be recycled back to the surface of the cell. Accordingly, on pathway **8**, receptor or molecule **30** with attached Seldeg **20** and target antigen-specific antibody 40 are cycled back to the surface of cell **10**. Target antigen-specific antibody 40 may then be released and may reattach from Seldeg **20** to the same or another Seldeg, or it may remain attached. Similarly, Seldeg **20** may then be released from receptor or molecule **30** and may reattach to the same or another cell surface receptor or molecule. For some Seldegs, the complex of Seldeg **20** and antibody 40 may dissociate from the receptor or other molecule **30** in the early or late endosome due to the acidic pH or low Ca^{2+} concentrations in this compartment (pathway C). Accordingly, in pathway D, receptor or cell surface molecule may recycle back to the cell surface whereas the Seldeg **20** bound to antibody 40 enters the lysosomes and is degraded into fragments **80** in pathway E. For some Seldegs, at some point following internalization into cell **10**, receptor or molecule **30** with attached Seldeg **20** and target antigen-specific antibody 40 enters the late endosomal/lysosomal in pathway F, in which at least target antigen-specific antibody 40 is degraded into fragments **80**. This entry into lysosomes is expected to be increased if Seldeg **20** cross-links receptor or molecule **30** into dimers or higher order aggregates.

Through this mechanism of selective depletion, Seldegs target and selectively deplete antigen-specific antibodies from the body without adversely affecting the levels of antibodies of non-targeted specificities.

In particular, Seldegs as described herein can target and selectively deplete antigen-specific antibodies from the body without having an adverse clinical effect in the patient due to the depletion of antibodies of non-targeted specificities Such adverse clinical effects include, for example, immunosuppression, and symptoms thereof, such as pinkeye, bronchitis, ear infections, sinus infections, cold, diarrhea, pneumonia, yeast infection, meningitis, skin infections, and other opportunistic infections, particularly opportunistic infection normally controlled through antibody mediated immune responses; and blood disorders, such as low platelet counts or anemia, and hypogammaglobulinemia and symptoms thereof, such as abdominal pain, bloating, nausea, vomiting, diarrhea, or weight loss.

In general, Seldegs according to this disclosure are configured to specifically bind a cell surface receptor/molecule at near-neutral pH via a targeting component and also specifically bind to an antigen-specific antibody at near-neutral pH via an antigen component that is fused directly or indirectly to the targeting component. The term "specifically bind" as used herein refers to a detectable selective intermolecular interaction between the targeting component and the cell surface receptor/molecule, or between the antigen component and the antigen-specific antibody. For example,

to specifically bind, the antigen needs to show a detectable interaction with the antibodies that are being targeted, whilst not showing a detectable interaction with other antibodies. Techniques for detecting specific binding are known within the art, such as ELISA, surface plasmon resonance analyses and other methods identifiable by skilled persons.

Accordingly, Seldegs allow at least a portion of the antigen-specific antibody in the circulation of a patient to be internalized into cells that express the targeted cell surface receptor or targeted other cell surface molecule and thereafter intracellularly degraded.

Seldegs according to this disclosure may avoid immune responses by containing one copy, otherwise referred herein as "one molecule", of each type of antigen, antigen fragment or antigen mimetic, per Seldeg, which in combination with the insertion of mutations to reduce or eliminate Fc gamma receptor binding and/or complement binding, is expected to decrease antibody cross-linking and the formation of potentially inflammatory immune complexes. In particular, at least 99% of Seldegs, at least 99.5% of Seldegs., or at least 99.9% of Seldegs may contain only one copy of antigen, antigen fragment, or antigen mimetic per Seldeg at near-neutral pH. Other Seldegs according to the present disclosure can contain more than one molecule of an antigen, antigen fragment, or antigen mimetic. The bivalent nature of the antibodies that are bound by Seldegs that contain one molecule of antigen per Seldeg molecule may result in complexes of two Seldeg molecules per antibody, which through target receptor dimerization is expected to increase the efficiency of lysosomal delivery of Seldeg-antibody complexes.

Seldegs can include at least a first antigen component and a second antigen component, wherein the one molecule of the antigen, antigen fragment or antigen mimetic of the first antigen component is different to the one molecule of the antigen molecule, antigen fragment or antigen mimetic of the second antigen component. Accordingly, Seldegs comprising at least a first antigen component and a second antigen component allow clearance of antigen-specific antibodies of more than one specificity.

Seldegs can include at least a first antigen component and a second antigen component, wherein the one molecule of the antigen, antigen fragment or antigen mimetic of the first antigen component is the same as the one molecule of the antigen molecule, antigen fragment or antigen mimetic of the second antigen component.

Accordingly, Seldegs can include, for example, one or more antigen components fused to a C-terminus and/or an N-terminus of a targeting component, wherein the one molecule of the antigen, antigen fragment or antigen mimetic antigen components of the respective antigen components can be the same or different.

In addition, Seldegs may contain human or humanized proteins or protein fragments to avoid or decrease the possibility of an immune reaction to the Seldeg when administered to a human. The antigen, antigen fragment, or antigen mimetic of the antigen component is preferably a human protein or protein fragment for administration of the Seldeg to a human. The targeting component is also preferably a human protein or protein fragment, such as a human antibody fragment or human albumin or albumin fragment, or a humanized antibody or humanized antibody fragment for administration of the Seldeg to a human. If a Seldeg is developed for use in a non-human animal, then proteins or protein fragments derived from or engineered to be immunologically compatible with that animal may be used instead.

FIG. **2**A is a schematic representation of the activity of a Seldeg **20***a* including antigen **100** fused to a targeting component having the Fc fragment of IgG 110. As understood by persons skilled in the art, the Fc fragment of an IgG is all of the lower base of the antibody's Y-shape, which is the sulfhydryl-bridged hinge region and the CH2 and CH3 domains. Seldegs can have an Fc fragment that does not have the hinge region, or the hinge region does not have sulfydryl bridges. Fc fragment **110** allows Seldeg **20***a* to bind an FcRn molecule on an FcRn-expressing cell. In the example shown in FIG. **2**A, antigen **100** may be fused to Fc fragment **110***a* at the N-terminus of the hinge-CH_2—CH_3 **120**. When antigen **100** is fused to Fc fragment **110***a* and the resulting antigen-Fc fragment dimerizes with another Fc fragment **110***b* lacking an antigen, using the knobs-into-holes strategy (for example, as described in Moore, G. L., Bautista, C., Pong E., Nguyen, D. H., Jacinto, J., Eivazi, A., Muchhal, U. S., Karki, S., Chu, S. Y., Lazar, G. A., 2011). A novel bispecific antibody format enables simultaneous bivalent and monovalent co-engagement of distinct target antigens. MAbs 3, 546-557), a heterodimeric Seldeg molecule **20***a* as shown is produced. Seldeg **20***a* has an Fc fragment with a monomeric display of antigen **100**, which avoids the formation of multimeric immune complexes that can cause inflammation and other adverse effects. Although Seldegs containing only antigen **100** fused to Fc fragment **110***a* may be produced and used in some circumstances, due to the tendency of an Fc fragment to dimerize, a dimer will typically be produced. In order to avoid Fc fragment dimers in which both Fc fragments **110***a* have a fused antigen **100**, which can lead to the formation of multimeric immune complexes, Seldegs are designed with knobs-into-holes mutations and/or electrostatic steering mutations (for example, as described in Gunasekaran, K., Pentony, M., Shen, M., Garrett, L., Forte, C., Woodward, A., Ng, S. B., Born, T., Retter, M., Manchulenko, K., Sweet, H., Foltz, I. N., Wittekind, M., Yan, W. (2010) Enhancing antibody Fc heterodimer formation through electrostatic steering effects: applications to bispecific molecules and monovalent IgG. J. Biol Chem 285, 19637-19646) to promote heterodimer formation, so there is only one Fc with one antigen fused. Other approaches can also be used to generate heterodimers, such as the insertion of a $(G_4S)_{13}$ linker peptide between the C-terminus of the antigen-Fc fusion and N-terminus of a second Fc fragment (for example, as described in Zhou, L., Wang, H Y., Tong, S., Okamoto, C. T., Shen, W C., Zaro, J. L. (2016) Single chain Fc-dimer-human growth hormone fusion protein for improved drug delivery. Biomaterials, 117, 24-31). DNA and protein sequences of several examples of Seldegs comprising knobs-into-holes mutations, electrostatic steering mutations, and/or arginine mutations or other mutations that reduce Fc gamma receptor and complement binding are described in Example 10.

Additional examples of knobs-into-holes mutations include Y349T/T394F:S364H/F405A and Y349T/F405F:S364H/T394F (for example as described in Moore, G. L., Bautista, C., Pong, E., Nguyen, D. H., Jacinto, J., Eivazi, A., Muchhal, U.S., Karki, S., Chu, S. Y., Lazar, G. A. (2011) A novel bispecific antibody format enables simultaneous bivalent and monovalent co-engagement of distinct target antigens. MAbs 3, 546-557) and T366W:T366S:L368A/Y407V (for example as described in Atwell, S., Ridgway, J. B. B., Wells, J. A., Carter, P (1997) Stable heterodimers from remodeling the domain interface of a homodimer using a phage display library. J. Mol. Biol., 270, 26-35) among others identifiable by persons skilled in the art. The residue numbering of these exemplary knobs into holes mutations

refers to the EU antibody numbering system, as would be understood by persons skilled in the art.

Additional examples of electrostatic steering mutations include E356K/D399K:K392D/K409D and K409D/K370D: D357K/D399K (for example as described in Gunasekaran, K., Pentony, M., Shen, M., Garrett, L., Forte, C., Woodward, A., Ng, S. B., Born, T., Retter, M., Manchulenko, K., Sweet, H., Foltz, I. N., Wittekind, M., Yan, W. (2010). Enhancing antibody Fc heterodimer formation through electrostatic steering effects: applications to bispecific molecules and monovalent IgG. J. Biol Chem 285, 19637-19646) among others identifiable by persons skilled in the at. The residue numbering of these exemplary electrostatic steering mutations refers to the EU antibody numbering system, as would be understood by persons skilled in the art.

Additional examples of arginine mutations or other mutations to reduce binding to Fc gamma receptors and complement (C1q) include G236R/L328R (for example as described in Horton, H. M., Bernett, M. J., Pong, E., Peipp, M., Karki, S., Chu, S. Y., Richards, J. O., Vostiar, I., Joyce, P. F., Repp, R., Desjarlais, J. R., Zhukosky, E. (2010) Potent in vitro and in vivo activity of an Fc-engineered anti-CD19 monoclonal antibody against lymphoma and leukemia. Cancer Res., 68, 8049-8057; Moore, G. L., Bautista, C., Pong, E., Nguyen, D. H., Jacinto, J., Eivazi, A., Muchhal, U. S., Karki, S., Chu, S. Y., Lazar, G. A. (2011). A novel bispecific antibody format enables simultaneous bivalent and monovalent co-engagement of distinct target antigens. MAbs 3, 546-557), N297A or N297Q (for example as described in Tao, M H., Morrison, S. L. (1989) Studies of aglycosylated chimeric mouse-human IgG: role of carbohydrate in the structure and effector functions mediated bu the human IgG constant region. J Immunol., 143, 2595-2601; Lux. A., Yu, X., Scanlan, C. N., Nimmerjahn, F. (2013) Impact of immune complex size and glycosylation on IgG binding to human FcγRs. J. Immunol., 190, 4315-4323), D265A (for example as described in Lux, A., Yu, X., Scanlan, C. N., Nimmerjahn, F (2013) Impact of immune complex size and glycosylation on IgG binding to human FcγRs. J. Immunol, 190, 4315-4323; Clynes, R. A., Towers, T. L., Presta, L. G., Ravetch, J. V. (2000) Inhibitory Pc receptors modulate in vivo cytotoxicity against tumor targets. Nat. Med. 6, 443-446). L234A/L235A (for example as described in Wines, B. D., Powell, M. S., Parren, P. W. H. I., Barnes, N., Hogarth, P. M. (2000) The IgG Fc contains distinct Fc receptor (FcR) binding sites: the leukocyte receptors FcγRI and FcγRIIa bind to a region in the Fc distinct from that recognized by neonatal FcR and protein A. J. Immunol., 164, 5313-5318), and L234A/L235A/P329G (for example as described in Schlothauer, T., Herter, S., Koller, C. F., Grau-Richards, S., Steinhart, V., Spick, C., Kubbies, M., Klein, C., Umana, P., Mossner, E. (2016) Novel human IgG1 and IgG4 Fc-engineered antibodies with completely abolished effector functions PEDS, 29, 457-466), among others identifiable by persons skilled in the art. The residue numbering of these exemplary arginine mutations or other mutations to reduce binding to Fc gamma receptors and complement (C1q) refers to the EU antibody numbering system, as would be understood by persons skilled in the art.

Other mutations to ablate FcγR and/or complement binding that target residues at, or in proximity to, the location of the FcγR and complement binding sites can be used. These sites on the Fc region of IgG have been localized (for example, as described in Jefferis, R., Lund, J. (2002) Interaction sites on human IgG-Fc for FcγR: current models. Immunol. Letts., 82, 57-65; Duncan, A. R., Winter. G (1988) The binding site for C1q on IgG. Nature, 332, 738-740; Idusogie, E. E., Presta, L. G., Gazzano-Santoro, H., Totpal, K., Wong, P. Y., Ultsch, M., Meng, G., Mulkerrin, M. G. (2000) Mapping of the C1q binding site on rituxan, a chimeric human antibody with a human IgG1 Fc. J. Immunol., 164, 4178-4184; Hogarth, P. M., Anania, J., Wines, B. D. (2014) The FcγR of humans and non-human primates and their interaction with IgG: implications for induction of inflammation, resistance to infection and the use of therapeutic monoclonal antibodies. Cur. Top. Microbiol. Immunol., 382, 321-352).

Seldegs may include Fc fragments derived from immunoglobulin classes or isotypes that do not bind, or have very weak binding, to Fc gamma receptors or complement such as human IgG2 or human IgG4.

For some applications such as diagnostic imaging, Seldegs may include Fc fragments with binding sites for Fc gamma receptors and/or complement to increase inflammatory responses against the antigen that is present in the Seldeg.

Fc fragment **110** may be modified to substantially increase its binding affinity for FcRn at near-neutral pH as compared to unmodified Fc fragments. For example, the dissociation constant between Fc fragment **110** and FcRn at a pH greater than 6.8 and less than 7.5 may be less than 10 μM as determined by surface plasmon resonance or other biophysical method. However, Fc fragment **110** may have a similar or increased affinity for FcRn as compared to an unmodified Fc fragment at acidic endosomal pH (about 6.0), or it may be modified to have a much lower or negligible binding affinity for FcRn at endosomal pH as compared to an unmodified Fc fragment. This increase in binding affinity at near neutral pH allows each Seldeg to cause its bound target antigen-specific antibody to be efficiently internalized and trafficked into late endosomes or lysosomes in FcRn-expressing cells. Enhanced binding affinity of the Fc fragment for FcRn may be achieved by insertion of mutations. Naturally-occurring IgGs have a substantially higher binding affinity for FcRn at acidic pH levels as opposed to near-neutral pH. This property is essential for the recycling and transport of IgG within FcRn-expressing cells. In contrast, an increase in binding affinity for FcRn at pH 7.4, for example, results in receptor-mediated internalization into cells and lysosomal delivery.

Fc fragment **110** may also be modified to eliminate or substantially reduce the binding affinity for Fc gamma receptors and complement (C1q). This modification prevents inflammatory responses caused by the formation of multimeric immune complexes. For example, as described in Example 10, the Fc regions can be mutated (G236R/L328R; EU numbering) (for example as described in Moore, G. L., Bautista, C., Pong, E., Nguyen, D. H., Jacinto, J., Eivazi, A., Muchhal, U. S., Karki, S., Chu, S. Y., Lazar, G. A. (2011). A novel bispecific antibody format enables simultaneous bivalent and monovalent co-engagement of distinct target antigens. MAbs 3, 546-557) (EU numbering), herein also referred to as "arginine mutations", so that they do not bind Fc gamma receptors. In Example 10, these mutations correspond to residues **22** and **114** of Fc-Syt1 (see SEQ ID NO: 10), and residues **144** and **236** of MOG-Seldeg-PS (see SEQ ID NO: 8). Other examples of mutations that substantially reduce or ablate binding to Fc gamma receptors and complement include N297A or N297Q (E U numbering; for example as described in Tao, M H., Morrison, S. L. (1989) Studies of aglycosylated chimeric mouse-human IgG: role of carbohydrate in the structure and effector functions mediated by the human IgG constant region. J. Immunol., 143, 2595-2601; Lux, A., Yu, X., Scanlan, C. N., Nimmerjahn, F.

(2013) impact of immune complex size and glycosylation on IgG binding to human FcγRs. J. Immunol., 190, 4315-4323), D265A (E U numbering; for example as described in Lux, A., Yu, X., Scanlan, C. N., Nimmerjahn, F. (2013) Impact of immune complex size and glycosylation on IgG binding to human FcγRs. J. Immunol., 190, 4315-4323; Clynes, R. A., Towers, T. L., Presta, L. G., Ravetch, J. V. (2000) Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. Nat. Med. 6, 443-446), L234A/L235A (EU numbering; for example as described in Wines, B. D., Powell, M. S., Parren, P. W. H. I., Barnes, N., Hogarth, P. M. (2000) The IgG Fc contains distinct Fc receptor (FcR) binding sites: the leukocyte receptors FcγRI and FcγRIIa bind to a region in the Fc distinct from that recognized by neonatal FcR and protein A. J. Immunol., 164, 5313-5318), L234A/L235A/P329G (EU numbering; for example as described in Schlothauer, T., Herter, S., Koller, C. F., Grau-Richards, S., Steinhart, V., Spick, C., Kubbies, M., Klein, C., Umana, P., Mossner, E. (2016) Novel human IgG1 and IgG4 Fc-engineered antibodies with completely abolished effector functions. PEDS, 29, 457-466), among others identifiable by persons skilled in the art. A reduction in binding affinity for Fc gamma receptors of at least 10-fold is preferred.

As shown in FIG. **2**B, in Seldeg **20***b* antigen **100** may be attached to Fc fragment **110***a* at another terminal location, or as shown in FIG. **2**C, in Seldeg **20***c*, antigen **100** may be attached at a non-terminal location. Any location that does not prevent specific FcRn binding is suitable. Such locations include amino acid residues that are sufficiently distant from the FcRn interaction site (encompassing residues **252-256**, **309-311**, **433-436** at the CH2-CH3 domain interface; EU numbering) so as not to either directly or sterically block FcRn binding, as would be identifiable by skilled persons.

Antigen **100** may be fused to Fc fragment **110** in any suitable manner, including attachment via a chemical reaction, attachment through a linker, or during formation of a single combined antigen-Fc fragment protein. Examples of chemical coupling that could be used are: amine-to-amine (NHS esters), sulfhydryl-to-sulfhydryl (maleimide), amine-to-sulfhydryl (NHS ester/maleimide), sulfhydryl-to-carbohydrate (maleimide/hydrazide), or attachment via an unnatural amino acid with the desired chemical reactivity. This unnatural amino acid can be inserted during recombinant production of the Fc fragment and/or antigen. Polyethyleneglycol (PEG) spacers can also be inserted between the chemically conjugated proteins, protein fragments or other molecules. Possible linkers include repeats of glyine-serine linker peptides, or other more rigid linker peptides, that are encoded in the recombinant expression plasmid for the antigen-Fc fusion. Linkage chemistry, sites of linkage and choice of peptide can be guided by molecular modeling, and can be designed to minimize loss of binding activity of the antigen or the protein/protein fragment targeting the cell surface molecule, as would be understood by skilled persons.

FIG. **2**D is a schematic representation of Seldeg **20***d* in which antigen **100** is attached to antibody variable region **130**. Antibody variable region **130** specifically binds to a cell surface receptor or cell surface molecule. Antibody variable region **130** may be an entire variable region or a fragment thereof, so long as it can specifically bind to a cell surface receptor or cell surface molecule. Antibody variable region **130** may include portions of a non-variable region of an antibody that is configured to bind to a cell surface receptor or cell surface molecule. For example, antibody variable region **130** may be a single-domain antibody (sdAb) or camelid-derived VHH domain (also commonly referred to as a nanobody). Such variable regions have the overall fold of an immunoglobulin domain, comprising two anti-parallel β-sheets, and can also include domains from other members of the immunoglobulin superfamily such as T cell receptor variable domains, constant region domains of antibodies or domains of the coreceptor, CD4, among others identifiable by persons skilled in the art. Antibody variable region **130** may be present as a monomer as shown in FIG. **2**D, or as a multimer. For example, if antibody variable region **130** is present as a nanobody, it may be engineered with a linker peptide such as GSSGGSGGGGS (SEQ ID NO: 35) between the C-terminus of the first nanobody and the N-terminus of the second nanobody to form a dimer, resulting in increased binding avidity for target receptor/molecule. If antibody variable region **130** is a nanobody or another protein that is engineered to form multimers, variants without antigen **100** may be included during Seldeg formation so that multimers contain only one copy of antigen **100**, just as described above for Seldegs containing Fc fragments. Antibody variable regions can also include heterodimers of heavy chain variable (VH) domains linked by peptide linkers to light chain variable (VL) domains to form scFv fragments. The linker sequences that are used to link VH and VL domains are well known to those with skill in the art and include the GGGGSGGGGSGGGGS [$(G_4S)_3$] (SEQ ID NO: 36) sequence that connects the C-terminus of the VH domain to the N-terminus of the VL domain. In some embodiments, the C-terminus of the VL domain can be connected to the N-terminus of the VH domain with similar linker sequences. ScFvs that bind to a cell surface receptor or other cell surface molecule can be isolated from libraries of scFvs using phage display, yeast display or other antibody display approaches. The targeting protein component of a Seldeg could also include Fab fragments of an antibody that can be isolated from libraries of Fab fragments using phage display, yeast display etc. For nanobodies, scFvs and Fab fragments, affinities for binding to a cell surface receptor or cell surface molecule can be increased by randomly mutating residues in the complementarity determining regions (CDRs), or by using error-prone polymerase chain reaction, to generate libraries of mutated nanobodies or variable domains. Exemplary CDR residues that would be targeted are those in CDR3 of the light chain variable domain (residues **89-97**; Kabat numbering) and CDR3 of the heavy chain variable domain (residues **95-102**; Kabat numbering). These libraries can be displayed on phage or yeast and higher affinity variants selected using approaches known to those with skill in the art.

Although FIG. **2**D illustrates antigen **100** at a terminal location of antibody variable region **130**, it may instead be located at a non-terminal location. Antigen **100** may be fused to antibody variable region **110** in any suitable manner, including attachment via a chemical reaction, attachment through a linker, or during formation of a single combined antigen-antibody variable region fusion protein.

A Seldeg may also contain an antigen component fused to targeting component that includes a protein other than an antibody or antibody fragment, providing that this protein is configured to bind to a cell surface receptor or other cell surface molecule. For example, as shown in FIG. **2**E, Seldeg **20***e* includes antigen **100** fused to albumin or an albumin fragment **140** able to bind FcRn. The albumin or albumin fragment may be mutated or modified so that it binds with increased affinity to FcRn. For example, mutations can be inserted into the FcRn binding domain (DIII) of (human serum) albumin using error prone PCR followed by display of libraries of mutated albumin variants on yeast or phage,

and selection of higher affinity variants. Alternatively, higher affinity variants can be generated by mutating residues at or near the albumin:FcRn interface and either selecting or screening for albumin variants with increased binding affinity. Although FIG. **2**E illustrates antigen **100** at a non-terminal location of albumin or albumin fragment **140**, it may instead be located at a terminal location. Antigen **100** may be fused to albumin or albumin fragment **140** in any suitable manner, including attachment via a chemical reaction, attachment through a linker, or during formation of a single combined antigen-FcRn-binding protein.

FIG. **2**F is a schematic representation of exemplary Seldeg **20***f* including antigen **100** attached to the N-terminus of an Fc fragment **150**. In the example shown in FIG. **2**F, protein or protein fragments **160** that bind to a cell surface receptor or cell surface molecule are attached to the C-terminus of Fc fragment **150***a*. For example, the protein or protein fragment may be the C2A domain of synaptotagmin that binds to phosphatidylserine (PS). Fc fragment **150** can be engineered to bind to FcRn with increased affinity and may be mutated so that it binds to Fc gamma receptors and complement with very low or no detectable binding affinity. In order to avoid Fc fragment homodimers having two Fc fragments **150***a* with fused antigen **100**, which can lead to the formation of multimeric immune complexes, Seldegs as shown in FIG. **2**F are designed with knobs-into-holes mutations and/or electrostatic steering mutations to promote heterodimer formation, so there is only one Fc with one Fc-antigen. In FIG. **2**F, both Fc fragments **150***a* and **150***b* have proteins or protein fragments that bind to the cell surface protein or other cell surface molecule fused to them; alternatively, only one such protein or protein fragment may be present. In the exemplary Seldeg shown in FIG. **2**G, the antigen **100** and protein or protein fragments **160** that bind to a cell surface receptor or cell surface molecule are fused to the C- and N-termini of the Fc fragments **150***a* and **150***b*, respectively, to generate Seldeg **20***g*.

FIG. **2**H is a schematic representation of exemplary Seldeg **20***h* including antigen **100** attached to the C-terminus of an antibody 170 that binds to a cell surface protein or cell surface molecule. The Fc fragment (Fc) in the antibody can be engineered to bind to FcRn with increased affinity and may be mutated so that it binds to Fc gamma receptors and complement with very low or no detectable binding affinity. In order to avoid antibody homodimers in which both Fc fragments have a fused antigen **100**, which can lead to the formation of multimeric immune complexes, Seldegs as shown in FIG. **2**H are designed with knobs-into-holes mutations and/or electrostatic steering mutations to promote heterodimer formation, so there is only one antibody heavy chain per antibody molecule with attached antigen **100**. Both Fab fragments of the antibody may bind to the same cell surface protein or other cell surface molecule; alternatively, they could bind to two or more different cell surface proteins or molecules.

FIG. **2**I is a schematic representation of exemplary Seldeg **20***i* comprising antigen **100** attached to the C-terminus of a scFv (180)-Fc fusion that binds to a cell surface protein or cell surface molecule. The Fc fragment (Fc) in the antibody can be engineered to bind to FcRn with increased affinity and may be mutated so that it binds to Fc gamma receptors and complement with very low or no detectable binding affinity. In order to avoid antibody homodimers in which both Fc fragments have a fused antigen **100**, which can lead to the formation of multimeric immune complexes, Seldegs as shown in FIG. **2**I are designed with knobs-into-holes mutations and/or electrostatic steering mutations to promote heterodimer formation, so there is only one antibody heavy chain-scFv fusion per molecule with attached antigen **100**. Both scFv fragments of the antibody may bind to the same cell surface protein or other cell surface molecule; alternatively, they could bind to two or more different cell surface proteins or molecules.

FIG. **2**J is a schematic representation of exemplary Seldeg **20***j* comprising antigen **100** attached to the N-terminus of an -Fc-scFv (180) fusion that binds to a cell surface protein or cell surface molecule. The Fc fragment (Fc) in the antibody can be engineered to bind to FcRn with increased affinity and may be mutated so that it binds to Fc gamma receptors and complement with very low or no detectable binding affinity. In order to avoid antibody homodimers in which both Fc fragments have a fused antigen **100**, which can lead to the formation of multimeric immune complexes, Seldegs as shown in FIG. **2**.**1** are designed with knobs-into-holes mutations and/or electrostatic steering mutations to promote heterodimer formation, so there is only one antibody heavy chain-scFv fusion per molecule with attached antigen **100**. Both scFv fragments of the antibody may bind to the same cell surface protein or other cell surface molecule; alternatively, they could bind to two or more different cell surface proteins or molecules.

As shown in FIG. **2**K, in exemplary Seldeg **20***k* two antigen components (**100**, **190**) may be attached to a targeting component, for example Fc fragment **110***a* and Fc fragment **110***b* at an N-terminal or other location to generate a Seldeg that can clear antigen-specific antibodies of different specificities. Seldegs as shown in FIG. **2**K are designed with knobs-into-holes mutations and/or electrostatic steering mutations to promote heterodimer formation, so there is an antigen molecule of each type (100, 190) in each Seldeg molecule.

FIG. **2**L is a schematic representation of exemplary Seldeg **20***l* comprising antigen **100** and antigen **190** attached to the N-termini of an Fc fragment **150**. In the exemplary embodiment shown in FIG. **2**L, protein or protein fragments **160** that bind to a cell surface receptor or cell surface molecule are attached to the C-termini of Fc fragment **150***a* and **150***b*. Seldegs as shown in FIG. **2**L are designed with knobs-into-holes mutations and/or electrostatic steering mutations to promote heterodimer formation, so there is an antigen molecule of each type (100, 190) in each Seldeg molecule. In FIG. **2**L, both Fc fragments **150***a* and **150***b* have proteins or protein fragments that bind to the cell surface protein or other cell surface molecule fused to them, but in other embodiments, only one such protein or protein fragment may be present.

As shown in FIG. **2**M, in exemplary Seldeg **20***m* two molecules of the same antigen (**100**) may be attached to Fc fragment **200** at N-terminal or other locations to generate exemplary Seldeg **20***m*. This exemplary Seldeg is a homodimer that contains mutations to enhance binding to FcRn, and does not contain knobs-into-holes and/or electrostatic steering mutations.

FIG. **2**N is a schematic representation of exemplary Seldeg **20***n* comprising two molecules of the same antigen (**100**) attached to the N-termini of an Fc fragment **210**. In the exemplary embodiment shown in FIG. **2**N, protein or protein fragments **160** that bind to a cell surface receptor or cell surface molecule are attached to the C-terminus of Fc fragment **210**. This exemplary Seldeg is a homodimer and does not contain knobs-into-holes and/or electrostatic steering mutations. In FIG. **2**N, the homodimeric Fc fragment **200** has proteins or protein fragments that bind to the cell surface protein or other cell surface molecule fused to both

polypeptide chains, but in other embodiments, only one such protein or protein fragment may be present.

For Seldegs that target FcRn, similar principles may be applied to other proteins able to bind FcRn. In addition, the FcRn-targeting Seldeg or methods of forming it may be affected by properties of the FcRn-binding protein. Although albumin tends to not form dimers or other multimers, other FcRn-binding proteins may, in which case the final Seldeg may be formed in a manner to those containing antibody fragments so that each Seldeg contains only one copy of the antigen. In the examples shown in FIG. **2**A, **2**B, **2**C, **2**F, **2**G, **2**H, **2**I, **2**J, **2**K, **2**L, the Seldeg has two antibody Fc fragments that are engineered with knobs-into-holes mutations and/or electrostatic steering mutations to drive the formation of heterodimers comprising one antigen linked to one Fc fragment and one Fc fragment with no antigen attached. The Fc fragment can be further engineered to bind to FcRn with increased affinity at near neutral pH (FIG. **2**A, **2**B, **2**C, **2**K, **2**M) or connected to one or more proteins, scFv fragments. Fab fragments or other molecules that target one or more cell surface receptors or molecules (FIGS. **2**F, **2**G, **2**H, **2**I, **2**J, **2**L, **2**N). The Fc fragments in the examples shown in FIG. **2**F, **2**G, **2**H, **2**I, **2**J, **2**L, **2**N can also be engineered to bind with higher affinity to FcRn so that they target both FcRn and one or more cell surface receptors or molecules.

Albumin binds more strongly to FcRn at acidic pH than at neutral pH. However, albumin may also be modified to alter its binding affinities at near-neutral or endosomal pH to encourage degradation of the target antigen-specific antibody and recycling of the Seldeg. Similarly, antibody variable region FcRn-binding proteins may be affected by pH in a manner specific to that protein, but they may still be modified to alter its binding affinities at near-neutral or endosomal pH to encourage degradation of the target antigen-specific antibody. These FcRn-binding proteins can be isolated from libraries of immunoglobulin variable domains, scFv (VH:VL heterodimers in which VH and VL domains are connected to each other by linker peptides such as GGGGSGGGGSGGGGS) (SEQ ID NO: 36) or Fab fragments using phage display, yeast display or other technologies known to those with skill-in-the-art. These libraries can either be derived from naturally occurring antibody variable genes, or can be generated using approaches that result in 'semi-synthetic' libraries wherein complementarity determining regions (CDRs) are produced using randomized oligonucleotide sequences. Further increases to their affinities can be achieved by, for example, inserting random mutations in the CDRs using error-prone PCR followed by selection using phage display or yeast display. Exemplary CDR residues that would be targeted are those in CDR3 of the light chain variable domain (residues **89-97**; Kabat numbering) and CDR3 of the heavy chain variable domain (residues **95-102**; Kabat numbering). Similar methods can be used to isolate antibody-based proteins or scaffold-based proteins that bind to other cell surface receptors/molecules.

Seldegs may include any targeting component that is configured to specifically bind to a receptor or other molecule on the cell surface (FIG. **2**D. **2**E. **2**F, **2**G, **2**H, **2**I, **2**J, **2**L or **2**N,). The targeting component is fused directly or indirectly (e.g., via a linker) to an antigen component having one molecule of each type of antigen, antigen fragment or antigen mimetic to reduce antibody-mediated crosslinking. The term "type of antigen" as used herein refers to an antigen that binds to a specific antibody. Accordingly, a Seldeg can include more than one antigen type, wherein each Seldeg has only one molecule of each antigen type. If the targeting protein contains an immunoglobulin-derived Fc fragment, the Fc region can be mutated so that it does not bind, or binds at substantially reduced levels, to Fc gamma receptors and complement. Several different possible configurations of Seldegs are shown in FIG. **2**A-N; these are shown as examples and are not limiting, since multiple other configurations can also be envisaged by those with skill-in-the-art.

Seldegs may include Fc fragments that bind to Fc gamma receptors and complement. The presence of the Fc gamma and complement binding sites may be desired in the context of particular application areas, when an immune response against the antigen in the Seldeg is desirable (for example, in tumor imaging). In such applications, Seldegs that are configured to bind to Fc gamma receptors and complement may be preferred. For example, Seldegs that include Fc fragments lacking engineered mutations to have decreased binding affinity or no binding affinity for Fc gamma receptors and/or complement (C1q) described herein, such as arginine mutations, may be configured to elicit such an immune response. Seldegs that include Fc fragments with mutations known to those with skill in the art to increase binding to Fc gamma receptors and or complement (C1q) may also be configured to elicit such an immune response. Such Seldegs may also be configured to comprise more than one antigen molecule per Seldeg (FIG. **2**K, **2**L, **2**M or **2**N) to enhance immune complex formation.

For example, Seldegs can have variations in numbers of targeting domains or antibody fragments (e.g. Fab fragments or scFv fragments) that range from 1-3 targeting domains or antibody fragments (FIG. **2**). These targeting domains or antibody fragments can be linked to immunoglobulin Fc fragments, whereas in others, the targeting domains or antibody fragments may be linked to each other; the antigen and antibody fragments can be fused to Fc fragments or each other in different orientations (FIG. **2**); Seldegs can include linker sequences that vary in length and composition between the fusion proteins, domains or fragments can be used e.g. IEGRMD (SEQ ID NO: 37), GGGGS (SEQ ID NO: 38) or 2-3 repeats of this linker; antigen mimetics such as small molecules or peptides can be used; the Fc fragment in Seldegs may be mutated so that it has substantially reduced binding affinity for Fc gamma receptors, complement, and increased affinity for binding to FcRn; The Fc fragments of a Seldeg may have mutations such as knobs-into-holes and/or electrostatic steering mutations so that heterodimers of antigen-linked and non-antigen-linked Fc fragments or containing two different antigens are formed.

Seldegs can include the following antigens that include proteins, glycoproteins and nucleic acids associated with autoimmune disease, including autoimmune encephalitides: myelin oligodendrocyte glycoprotein (MOG), myelin basic protein, proteolipid protein, myelin-associated glycoprotein, myelin-associated oligodendrocyte basic protein, transaldolase, acetylcholine receptor, muscle specific kinase, low density lipoprotein receptor related protein 4, insulin, islet antigen **2**, glutamic acid decarboxylase 65, zinc transporter 8, citrullinated antigens, carbamylated antigens, collagen, cartilage gp39, gp130-RAPS, 65 kDa heat shock protein, fibrillarin, small nuclear protein (snoRNP), aquaporin 4, thyroid stimulating factor receptor, nuclear antigens, DNA, histones, glycoprotein gp70, ribosomes, pyruvate dehydrogenase dehydrolioamide acetyltransferase, hair follicle antigens, human tropomyosin isoform 5, N-Methyl-D-aspartate (NMDA) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, $GABA_A$ and $GABA_B$ receptors, glycine receptor, dipeptidyl-peptidase-like protein 6 (DPPX), glutamate receptor (GluR5), voltage gated potas-

sium channel, Hu, Thyroid peroxidase, thyroglobulin, thyroid stimulating hormone (TSH) receptor, thyroid hormones T3 and T4, desmoglein 1 and 3, among others identifiable by skilled persons. The following antigens are examples of antigens that are associated with tumors and can be incorporated into Seldegs to clear tumor-specific antibodies during diagnostic imaging: HER2, prostate specific membrane antigen (PSMA), prostate stem cell associated antigen (PSCA), c-Met, EpCAM, carcinoembryonic antigen (CEA). Other antigens include therapeutics for which patients have specific antibodies, or transplantation antigens that are recognized by antibodies in transplant recipients. In addition, it is possible to generate molecular mimics (synthetic, protein fragments etc.) of antigens, and these can also be used to generate Seldegs. The above antigens are examples and are not limiting to additional types of possible antigens identifiable by persons skilled in the art upon reading of the present disclosure.

In several examples described herein, the Seldeg can be a heterodimer of fusion proteins comprising the amino acid sequences of SEQ ID NO: 2 plus SEQ ID NO: 6, SEQ ID NO: 4 plus SEQ ID NO: 6, SEQ ID NO: 8 plus SEQ ID NO: 10, SEQ ID NO: 12 plus SEQ ID NO: 14, SEQ ID NO: 16 plus SEQ ID NO: 18 plus the antibody light chain SEQ ID NO: 20, SEQ ID NO: 22 plus SEQ ID NO: 24 plus the antibody light chain SEQ ID NO: 20, SEQ ID NO: 26 plus SEQ ID NO: 28, SEQ ID NO: 30 plus SEQ ID NO: 6, SEQ ID NO: 32 plus SEQ ID NO: 6, or SEQ ID NO: 34 plus SEQ ID NO: 6, or homologs thereof.

The Seldeg can be a fusion protein comprising an amino acid sequence having at least 50%, identity with SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18. SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, or SEQ ID NO: 34.

As used herein, "sequence identity" or "identity" in the context of two nucleic acid or polypeptide sequences makes reference to the nucleotide bases or residues in the two sequences that are the same when aligned for maximum correspondence over a specified comparison window. When percentage of sequence identity or similarity is used in reference to proteins, it is recognized that residue positions which are not identical often differ by conservative amino acid substitutions, where amino acid residues are substituted with a functionally equivalent residue of the amino acid residues with similar physiochemical properties and therefore do not change the functional properties of the molecule.

A functionally equivalent residue of an amino acid used herein typically refers to other amino acid residues having physiochemical and stereochemical characteristics substantially similar to the original amino acid. The physiochemical properties include water solubility (hydrophobicity or hydrophilicity), dielectric and electrochemical properties, physiological pH, partial charge of side chains (positive, negative or neutral) and other properties identifiable to a person skilled in the art. The stereochemical characteristics include spatial and conformational arrangement of the amino acids and their chirality. For example, glutamic acid is considered to be a functionally equivalent residue to aspartic acid in the sense of the current disclosure. Tyrosine and tryptophan are considered as functionally equivalent residues to phenylalanine. Arginine and lysine are considered as functionally equivalent residues to histidine.

A person skilled in the art would understand that similarity between sequences is typically measured by a process that includes the steps of aligning the two polypeptide or polynucleotide sequences to form aligned sequences, then detecting the number of matched characters, i.e. characters similar or identical between the two aligned sequences, and calculating the total number of matched characters divided by the total number of aligned characters in each polypeptide or polynucleotide sequence, including gaps. The similarity result is expressed as a percentage of identity.

As used herein, "percentage of sequence identity" means the value determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide sequence in the comparison window may include additions or deletions (gaps) as compared to the reference sequence (which does not include additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison, and multiplying the result by 100 to yield the percentage of sequence identity.

As used herein, "reference sequence" is a defined sequence used as a basis for sequence comparison. A reference sequence may be a subset or the entirety of a specified sequence; for example, as a segment of a full-length protein or protein fragment A reference sequence can be, for example, a sequence identifiable in a database such as GenBank and UniProt and others identifiable to those skilled in the art.

As understood by those skilled in the art, determination of percent identity between any two sequences can be accomplished using a mathematical algorithm. Computer implementations of suitable mathematical algorithms can be utilized for comparison of sequences to determine sequence identity. Such implementations include, but are not limited to: CLUSTAL, ALIGN, GAP, BESTFIT, BLAST, FASTA, among others identifiable by skilled persons.

For example, Seldegs according to the present disclosure can have an amino acid sequence having at least 50% sequence identity, preferably at least 80%, more preferably at least 90%, most preferably at least 95% sequence identity compared to SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or SEQ ID NO: 10, or SEQ ID NO: 12, or SEQ ID NO: 14, or SEQ ID NO: 16, or SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, or SEQ ID NO: 34.

The antigen-specific antibodies that are targeted by Seldegs can be autoantibodies that are present in a patient, antibodies that bind to therapeutics, antibodies that recognize transplant and modified (e.g. radiolabeled) antibodies or fragments/engineered forms that are used in diagnostic imaging, among others identifiable by persons skilled in the art.

As shown in the examples below, Seldegs are able to selectively deplete target antigen-specific antibodies with specificity for their fused antigen, for example, the target antigen-specific antibodies HER2-specific trastuzumab or pertuzumab ("TZB" or "PZB") and MOG-specific antibody ("8-18C5") As shown in the examples below, Seldegs are able to selectively deplete the target antigen-specific antibodies without negatively affecting the total IgG levels or eliciting an adverse immune reaction. These findings stand in contrast to other approaches, in which treatment results in depletion of total IgGs, through the use of FcRn inhibitors or antibodies that destroy B-cells. Such approaches

adversely affect antibodies of non-targeted specificities or B-cell function because they lack the selectivity provided by Seldegs.

Based on this unique selectivity, the Seldeg platform has many applications because Seldegs may be created with many other targeting proteins and antigens. Examples of such applications include treatment of autoimmune disorders, treatment of antibody-mediated rejection prior to or during transplantation, increasing contrast during whole body imaging of tumors (e g., the tumor antigens PSMA, EpCAM, and CEA may be used as antigens for developing additional Seldegs), depleting the bodily concentration of a particular biologic after administration, for instance, if an adverse reaction is observed, removal of antibodies to clear antibodies that recognize a therapeutic prior to delivery of the therapeutic.

Seldegs may be administered in any way able to deliver them to cells expressing the receptor or other molecule on the cell surface that is being targeted, such as via injection, particularly intravenous, subcutaneous or intramuscular injection, or injection into a tissue targeted by the antigen-specific antibody that is to be depleted Seldegs can also be expressed in cells that have been genetically engineered to contain expression constructs encoding Seldegs. In particular, cells can be genetically engineered by introducing expression constructs that encode Seldeg proteins that include proteins or peptides that allow secretion of Seldegs from the engineered cells in situ. For example, patient-derived cells could be transfected with expression constructs encoding Seldegs and the transfected cells delivered back into the patient, using similar approaches to those described for chimeric antigen-receptor (CAR) T cell therapy. The expression constructs would comprise an expression vector known to those with skill in the art and may, for example, contain genes encoding MOG-Seldeg (SEQ ID NO: 1 and 5), with secretion leader peptides such as those derived from immunoglobulin genes linked to the 5' end of the coding sequence for the mature MOG-Seldeg (SEQ ID NO: 1) and Fc (SEQ ID NO: 5).

Seldegs may be administered in an amount that does not block every targeted receptor/cell surface molecule, allowing normal function of the cell surface receptor/molecule. The dose of Seldeg used may be similar to the amount of antibody being targeted for clearance, which will depend, for example, on the specifics of the antibody-mediated disease, or whether Seldegs are being used to improve contrast in diagnostic imaging. The amount of Seldeg used is expected to be less than the total number of receptor types being targeted, so that the normal function of the targeted receptor is not adversely affected. In addition, Seldegs can be designed so that they do not compete with the natural ligand of the cell surface receptor or cell surface molecule for binding, for example, by using nanobodies (VHH) that bind to FcRn at a site that does not overlap with the IgG binding site (for example as described in Andersen, J. T., Gonzalez-Pajuelo, M., Foss, S., Landsverk, O. J. B., Pinto, D., Szyroki, A., de Haard. H. J., Saunders, M., Vanlandshoot, P., Sandlie, I. (2012) Selection of nanobodies that target human neonatal receptor Sci. Rep., 3, 1118) In addition, Seldegs may remove less than 10%, less than 5%, less than 1%, or less than 0.1% of non-targeted antibodies in the circulation or in a tissue targeted by the antigen-specific antibody that is to be depleted. Retention of non-targeted antibodies during and after Seldeg treatment may be important in normal immune function and the avoidance of infections, among other effects as described herein.

Seldegs may be administered daily, weekly, or whenever 50% of patients are expected to have regenerated a threshold amount of targeted antigen-specific antibody in the circulation or in a tissue recognized by the targeted antigen-specific antibody. The levels of targeted antigen-specific antibody can be determined by using enzyme-linked immunosorbent assays (ELISAs) to analyze serum samples. Alternatively, other methods that are well known to those with skill in the art can be used.

In transplant patients at risk for antibody-mediated rejection, the Seldegs may be administered before or after transplantation. An emergency dose of Seldegs may be administered if the target antigen-specific antibody reaches a threshold amount of target antigen-specific antibody in the circulation or in a tissue recognized by the target antigen-specific antibody. The levels of targeted antigen-specific antibody can be determined by using enzyme-linked immunosorbent assays (ELISAs) to analyze serum samples. Alternatively, other methods that are well known to those with skill in the art can be used.

In patients that have antibodies specific for a therapeutic, such as a protein-based therapeutic, the Seldegs may be administered before the delivery of the therapeutic to deplete such antibodies. This is expected to overcome problems associated with rapid antibody-mediated clearance of therapeutics if they have elicited an immune response during prior delivery, or if preexisting antibodies specific for the therapeutic are present in the patient. Pre-existing or induced antibodies specific for the protein-based therapeutic can be detected using a number of different methods (for example such as those described in Xue, L., Clements-Egan, A., Amaravadi, L., Birchler, M., Gorovits, B., Liang, M., Myler, H., Purushothama, S., Manning, M. S., Sung, C. (2017) Recommendations for the assessment and management of pre-existing drug-reactive antibodies during biotherapeutic development. AAPS, 19, 1576-1586).

In diagnostic/theranostic imaging, it is expected that delivery of the radiolabeled imaging antibody will be followed by a period to allow tumor localization. Subsequently, Seldegs can be used to clear radiolabeled antibody from off-target sites (e.g. circulation) to result in improved contrast. For example, this approach can include the following steps' first, a patient is injected with radiolabeled (or other label) antibody that binds to a tumor antigen. Second, following a period (e.g. 16-24 hours) to allow the radiolabeled antibody to bind to the tumor, the Seldeg is injected in an amount that is equivalent in molar amounts to the injected dose of imaging agent. Following a clearance period (e.g. 4-24 hours), the patient is imaged using positron emission tomography or other whole body imaging modality.

The Seldeg may be administered in an amount sufficient to deplete at least 50%, at least 80% or at least 90% of the concentration of the target antigen-specific antibody in the circulation or in a tissue recognized by the target antigen-specific antibody within one hour, two hours, five hours, 24 hours or 48 hours or longer of administration. The persistence of the Seldeg in the body will be a determinant of how long it has activity in depleting antigen-specific antibody. Seldegs can be designed to have different in vivo half-lives by the behavior of the cell surface receptor or cell surface molecule that they target. The affinity of the Seldeg for this cell surface receptor or cell surface molecule can also be modified using mutagenesis and approaches known to those with skill in the art, to result in Seldegs that have different persistence in the circulation and/or tissues. In particular, the Seldeg may be administered in an amount at least approximately equimolar with the amount of antigen-specific anti-

body to be depleted. The Seldeg can be administered in an amount that is, for example, in an approximately 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1 or higher molar ratio to the target antigen-specific antibody. In particular, for example, wherein a Seldeg targets an antibody that is administered to a patient (e.g. anti-MOG, or anti-HER2 antibodies, and the like) a Seldeg can be administered in a dose that is for example, in an approximately 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1 or higher molar ratio to the administered target antigen-specific antibody.

EXAMPLES

The following examples are provided to further illustrate specific embodiments of the disclosure. They are not intended to disclose or describe each and every aspect of the disclosure in complete detail and should be not be so interpreted. Unless otherwise specified, designations of cell lines and compositions are used consistently throughout these examples.

Example 1—Expression and Purification of Seldegs that Bind to FcRN

Seldegs that target FcRn on cells contain a recombinant antigen as a monomer linked to a dimeric, human IgG1-derived Fc fragment (FIG. **3**A) with mutations to eliminate interactions with human FcγRs and to enhance the binding affinity of the Seldeg Fc fragment to FcRn at near-neutral pH Heterodimer formation of these two Seldegs is achieved by inserting 'knobs-into-holes' mutations in the CH3 domains.

Expression constructs to generate the exemplary HER2-Seldeg (SEQ ID NOS: 3, 4, 5 and 6) were made as follows: to express the polypeptide chain with HER2 fused to an engineered Fc fragment (SEQ ID NO: 3), the gene encoding the HER2 leader peptide and extracellular domain (ECD consisting of 630 residues) was isolated from a HER2-overexpressing breast cancer cell line (BT-474) employing standard molecular biology techniques. This gene was fused via a IEGRMD linker peptide to the N-terminus of the hinge region of a gene encoding the human IgG1-derived Fc fragment using splicing by overlap extension. Mutations to ablate binding to FcγRs (G236R/L328R; EU numbering), enhance binding to FcRn (MST-HN; M252Y/S254T/T256E/H433K/N434F; EU numbering) and generate 'knobs-into-holes' (Y349T/T394F; EU numbering) were inserted into the Fc fragment gene using standard methods. Cysteine (C220; EU numbering) in the hinge region that bridges with cysteine in the light chain constant region was also mutated to serine. Fc fragment genes with FcRn-enhancing mutations, mutations to ablate FcγR binding and without fused antigen were generated with complementary knobs-into-holes mutations (S364H/F405A; EU numbering) (SEQ ID NO: 5). Recombinant proteins were expressed in HEK-293F (Life Technologies) cells following transient transfection with the Gibco Expi293™ expression system kit (Life Technologies) The HER2-Seldeg was purified from culture supernatants using an anion exchange column (SOURCE-15Q, GE Healthcare) at pH 8.0 and a linear salt gradient (0-0.5 M NaCl). Alternatively, HER2-Seldeg can be purified using protein A-Sepharose and standard methods. Following elution from the column (ion exchange or protein A-Sepharose) HER2-Seldeg was dialyzed against phosphate buffered saline (PBS). HER2-Seldeg was further purified using size exclusion chromatography (SEC) (GE Healthcare) in PBS (Lonza) prior to use in experiments. Expression plasmids for other Seldegs were made using analogous methods, and recombinant proteins expressed in transfected HEK-293F cells. Seldegs without FcRn-enhancing mutations (e.g. MOG-Seldeg-PS, MOG-Seldeg-TfR; SEQ ID NOS: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20) were purified using protein G-Sepharose.

Seldegs targeting antibodies specific for two antigens were generated: (1) the HER2-Seldeg; and (2) the MOG-Seldeg. The antigen HER2 is a well-defined target for therapy and also for diagnostic imaging of HER2-overexpressing tumors with HER2-specific antibodies, such as trastuzumab (TZB) or pertuzumab (PZB). The antigen MOG is recognized by autoreactive antibodies in both animal models of multiple sclerosis (MS) and MS in humans.

The HER2-Seldeg and MOG-Seldeg maintain a significantly higher binding affinity for FcRn at neutral pH and at an acidic pH, in contrast to recombinant fusion proteins comprising HER2 or MOG fused to Fc fragments to generate analogous constructs ("HER2-WT" and "MOG-WT", respectively) to the HER2-Seldeg and MOG-Seldeg, except they lack the FcRn-enhancing MST-HN mutations (M252Y, S254T, T256E, H433K, N434F; EU numbering) that increase binding affinity at near-neutral pH (FIG. **3**B). Surface plasmon resonance experiments to analyze the interactions of the recombinant proteins with FcRn were carried out using a BIAcore T200 (GE Healthcare) Binding of Seldeg/WT to recombinant mouse FcRn was analyzed by injecting 100 nM MOG/HER2-Seldeg or MOG/HER2-WT over immobilized FcRn (coupled at ~600 RU on a CM5 sensor chip) in PBS (pH 6.0 or 7.4) plus 0.01% v/v Tween-20 at a flow rate of 10 μl/minute. Flow cells were regenerated following each injection and dissociation phase using 0.15 M NaCl, 0.1 M sodium bicarbonate, pH 8.5. Data were zero-adjusted and background-subtracted (background obtained by injection over a flow cell coupled with buffer only during coupling reaction).

Mutations to increase FcRn binding such as MST-HN were identified using the following approach: residues in proximity to amino acids (e.g. **253**, **435**) that are known to be essential for FcRn binding were randomly mutated in an Fc fragment gene and the libraries of mutated Fc fragments displayed on phage. Fc fragments with increased binding affinity for FcRn were selected using phage display technology (Ghetie, V., Popov, S., Borvak, J., Radu, C., Matesoi, D., Medesan, C., Ober, R. J., Ward, E. S. (1997) Increasing the serum persistence of an IgG fragment by random mutagenesis, Nature Biotech., 15, 637-640; Dall'Acqua, W. F., Woods, R. M., Ward, E. S., Palaszynski, S. R., Patel, N. K., Brrewah, Y. A., Wu, H., Kiener, P. A., Langermann, S. (2001) Increasing the affinity of a human IgG1 for the neonatal receptor: biological consequences, J. Immunol., 169, 5171-5180). Alternatively, these residues can be mutated to every other possible amino acid and Fc fragments with higher affinity for FcRn identified using methods such as ELISA or surface plasmon resonance binding analyses.

Size exclusion analyses indicate that the recombinant proteins comprising the Seldegs do not form aggregates following incubation in phosphate buffered saline when incubated for up to 30 days at 4° C. or 5 days at 37° C. (FIG. **3**C).

Example 2—Ability of Seldegs that Target FcRn to Deplete Target Antigen-Specific Antibodies in Mice that Transgenically Express Human FcγRs (huFcγR Mice)

To determine the ability of Seldegs to deplete target antigen-specific antibodies, mice that transgenically express

human FcγRs (huFcγR mice; Smith, P., DiLillo, D. J., Bournazos, S., Li, F., Ravetch, J. V. (2012). Mouse model recapitulating human Fcγ receptor structural and functional diversity. Proc. Natl. Acad. Sci. USA 109, 6181-6186. were injected with 15 μg of radiolabeled (^{125}I-labeled) MOG-specific antibody 8-18C5. 24-hours after the huFcγR mice were injected with 8-18C5, 125 μg or 31 μg of MOG-Seldeg or a control protein was administered via injection.

In FIG. **3**D, "MOG-Seldeg-High" corresponds to the 125 μg dose and "MOG-Seldeg-Low" corresponds to the 31 μg dose. The controls are phosphate-buffered saline ("PBS") and unmodified MOG-Fc fusion protein ("MOG-WT"). MOG-WT is an analogous construct to the MOG-Seldeg, except it lacks the FcRn-enhancing MST-HN mutations that increase binding affinity at near-neutral pH.

To generate the data of FIG. **3**D whole body counts of radiolabeled 8-18C5 were taken at the indicated times. Counts per minute ("CPM") obtained 24 hours after 8-18C5 administration, immediately prior to Seldeg or control delivery, are taken as 100% for each mouse and CPM of whole body obtained thereafter are normalized to this time point. The error bars indicate standard deviations and statistically significant differences were determined using two-way ANOVA with Tukey's multiple comparisons, with $p<0.05$ and n=6 mice/group.

Doses of 125 μg and 31 μg of MOG-Seldeg are approximately 2 to 8-fold lower (on a molar basis) than a dose of 500 μg, a MST-HN Abdeg, which has been shown to globally eliminate IgG levels in mice. Such lower doses of MOG-Seldeg were used to minimize effects on IgGs that were not specific for the fused antigen through competition with the Seldeg for FcRn binding. The doses of 125 μg or 31 μg represent an approximate 16 and 4-fold molar excess, respectively, over the 8-18C5 target antigen-specific antibody.

FIG. **3**D provides a graph of normalized body counts of radiolabeled 8-18C5 (the target antigen-specific antibody) versus time. Administration of MOG-Seldeg resulted in a rapid, dose-dependent decrease in 8-18C5 in normalized whole body counts (FIG. **3**D), which demonstrates the ability of MOG-Seldeg to selectively deplete 8-18C5 from the body. In contrast, the injection of control MOG-WT, lacking the FcRn-enhancing MST-HN mutations, had no effect on 8-18C5 antibody depletion. This demonstrates the importance of the MST-HN mutations to confer a high binding affinity for FcRn at pH 6.0-7.4.

Example 3—Specificity of Seldegs that Target FcRn and their Ability to Induce a Significant Decrease in Target Antigen-Specific Antibodies Levels, Both in Blood and Throughout the Body

To analyze the specificity of Seldegs and their effect on antibodies with different antigen recognition properties, the behavior of the HER2-specific antibody TZB was investigated in the presence of both HER2-Seldeg and MOG-Seldeg (FIG. **3**E). To generate the data of FIG. **3**E, huFcγR mice were intravenously injected with 15 μg of radiolabeled (^{125}I-labeled) TZB and subsequently with a 4-fold molar excess of HER2-Seldeg, or, as a control for antigen specificity, MOG-Seldeg. Additional controls are phosphate-buffered saline ("PBS"), Abdeg and a recombinant fusion protein comprising HER2 fused to an Fc fragment to generate an analogous construct ("HER2-WT") to the HER2-Seldeg, except it lacks the FcRn-enhancing MST-HN mutations that increase binding affinity at near-neutral pH. In contrast to a Seldeg, an "Abdeg" is a human IgG1-derived antibody with the MST-HN mutations that non-selectively depletes antibodies. Such proteins are called Abdegs because they are antibodies that generally cause IgG degradation.

To generate the data of FIG. **3**E, the mice were bled and blood and whole body counts were taken at the indicated times. Counts per minute ("CPM") obtained 24-hours after TZB administration, immediately prior to Seldeg or control delivery, are taken as 100% for each mouse and CPM of blood and whole body obtained thereafter are normalized to this time point. The error bars indicate standard deviations and statistically significant differences were determined using two-way ANOVA with Tukey's multiple comparisons, with $p<0.05$ and n=6 mice/group.

FIG. **3**E provides graphs of normalized blood and body counts of radiolabeled TZB (the target antigen-specific antibody) versus time. Administration of HER2-Seldeg caused a significant decrease in normalized body counts of TZB, both in blood and whole body counts, which demonstrates the ability of HER2-Seldeg to selectively deplete TZB from the body. In contrast, the control proteins demonstrated similar behavior to that observed for the PBS control (FIG. **3**E).

Example 4—Ability, of Seldegs that Target FcRn to Rapidly Deplete Target Antigen-Specific Antibodies

Mice were intravenously administered with radiolabeled (^{125}I) TZB (15 μg) and 24 hours later HER2-Seldeg (51 μg; four-fold molar excess over TZB) was delivered intravenously. Additional controls are phosphate-buffered saline ("PBS") and Abdeg (60 μg).

To generate the data of FIG. **3**F, the mice were bled and blood and whole body counts were taken at the indicated times. Counts per minute ("CPM") obtained 24-hours after TZB administration, immediately prior to Seldeg or control delivery, are taken as 100% for each mouse and CPM of blood and whole body obtained thereafter are normalized to this time point. The error bars indicate standard deviations and statistically significant differences were determined using two-way ANOVA with Tukey's multiple comparisons, with $p<0.05$ and n=5-6 mice/group.

FIG. **3**F provides graphs of normalized blood and body counts of radiolabeled TZB (the target antigen-specific antibody) versus time. Administration of HER2-Seldeg caused a rapid decrease in normalized body and blood counts of TZB, which demonstrates the ability of the HER2-Seldeg to rapidly deplete TZB from the body. Notably, the blood counts of TZB were reduced close to background levels within two hours of Seldeg administration (FIG. **3**F), further supporting the ability of the HER2-Seldeg to deplete target antigen-specific antibodies rapidly from the blood. In contrast, at a dose of 60 μg/mouse, delivery of Abdeg resulted in similar behavior to that observed for the PBS control (FIG. **3**F).

Example 5—Activity of Seldegs that Target Exposed Phosphatidylserine (PS) on the Cell Surface

We also investigated the ability of a Seldeg in which the targeting protein is the C2 domain of synaptotagmin 1 (Syt1) to selectively deplete antibodies specific for MOG in huFcγR mice. Syt1 binds to exposed PS on cells, and the Seldeg is therefore designed MOG-Seldeg-PS and is shown schematically (FIG. **4**A). MOG-Seldeg-PS(DN) that does not bind to PS due to the presence of the 'DN' mutations (D173N, D179N, D231N, D233N and D239N) was also

generated. MOG-Seldeg-PS and MOG-Seldeg-PS(DN) were purified from culture supernatants of transfected HEK-293F cells using protein G-Sepharose and standard methods Heterodimer formation was achieved by inserting knobs-into-holes and electrostatic steering mutations into the Fc regions, and size exclusion analyses indicate that the recombinant proteins are well behaved (FIG. **4**A).

To generate the data shown in FIG. **48**, mice were intravenously injected with radiolabeled (^{125}I) chimeric 8-18C5 (human constant/mouse variable domains; MOG-specific; 15-20 μg) and 24 hours later phosphate-buffered saline (PBS), 40 μg MOG-Seldeg-PS or as controls, 34 μg Fc-Syt1 (no MOO attached) or 40 μg MOG-Seldeg-PS(DN) were delivered intravenously. Radioactivity levels were determined at the indicated times Whole body CPM or blood CPM levels obtained immediately prior to MOG-Seldeg-PS or control delivery were taken as 100% and all subsequent CPM that were obtained were normalized against these CPM levels. Error bars indicate the standard error of the mean (SEM) and statistically significant differences between MOG-Seldeg-PS treated group and control groups (Fc-Syt1, MOG-Seldeg-PS(DN) and PBS) are indicated by * ($p<0.05$, two-way ANOVA with Tukey's multiple comparisons; n=5-6 mice/group).

Administration of MOG-Seldeg-PS caused a significant decrease in normalized body counts of 8-18C5, both in blood and whole body counts, which demonstrates the ability of MOG-Seldeg-PS to selectively deplete 8-18C5 from the body, in contrast, the control protein Fc-Syt1 demonstrated similar behavior to that observed for the PBS control, and although MOG-Seldeg-PS(DN) induced a decrease in 8-18C5 (due to residual binding to PS), the effect was much lower than that of MOG-Seldeg-PS (FIG. **4**B).

Example 6—Ability of Seldegs that Target FcRn to Efficiently Internalize Target Antigen-Specific Antibodies into Endosomes and Cause Degradation Via Delivery to Lysosomes

To determine the mechanism of activity of Seldegs at the cellular level, flow cytometry and fluorescence microscopy were performed to analyze the effects of Seldegs on the internalization and accumulation of target antigen-specific antibodies TZB, PZB and 8-18C5. First, human endothelial cells (HMEC-1) were transfected with a human FcRn-GFP expression construct, which was mutated so that its binding properties are analogous to mouse FcRn.

The Seldegs efficiently internalized bound target antigen-specific antibodies into endosomes within cells, and following 8 hours of incubation, the target antigen-specific antibodies were delivered to lysosomes.

FIG. **5**A is a graph of mean fluorescence intensity ("MFI") and FIG. **5**B and FIG. **5**C are microscopic images of Seldeg activity in the presence of target antigen-specific antibodies, with microscopic images of representative endosomes cropped, expanded, and presented in the top right-corner insets. FIGURE SA shows a greater MFI in the presence of, respectively, Alexa 647-labeled TZB with HER2-Seldeg and Alexa 647-labeled 8-18C5 with MOG-Seldeg. This greater MFI indicates that co-incubation of HER2- and MOG-Seldeg, respectively, with TZB and 8-18C5 (400 nM Seldeg or WT control plus 100 nM antigen-specific antibody; 30 minute pulse, no chase or 60 minute chase, labeled **30'** P or **30'** P, **60'** C, respectively, in FIGS. **5**A, **5**B and **5**C) results in high levels of TZB and 8-18C5 entering cells. Similar results were obtained when the HER2-specific antibody pertuzumab (PZB) was used instead of TZB in the presence of HER2-Seldeg (FIG. **5**A). Further, the majority of each target antigen-specific antibody is retained by the cells during a 60 minute chase. In contrast, the accumulation of target antigen-specific antibodies within cells is substantially lower in the presence of negative controls HER2-WT (selective for TZB or PZB) and MOG-WT (selective for 8-18C5).

FIGS. **5**B and C show that antigen-specific antibodies accumulate in cells and are associated with FcRn in endosomes in the presence of Seldegs. To generate the microscopic images of FIG. **5**B, HMEC-1 cells were pulsed with 100 nM Alexa 647-labeled TZB (HER2-specific) in complex with 400 nM Alexa 555-labeled HER2-Seldeg or HER2-WT (as indicated) for 30 minutes, washed and either immediately fixed, or washed, chased in medium for 60 minutes, followed by fixation. Fixed cells were imaged using fluorescence microscopy. The data in FIG. **5**C was generated using the same approach, except that 100 nM Alexa 647-labeled 8-18C5 (MOG-specific) in complex with 400 nM Alexa 555-labeled MOG-Seldeg or MOG-WT was used Bars in each of the microscopic images are 5 μm, and bars in each of the microscopic image insets are 0.25 μm. The data shown in FIGS. **5**B and **5**C demonstrates that antigen-specific antibodies accumulate to substantially higher levels in FcRn-expressing cells in the presence of Seldegs that bind to FcRn compared with in the presence of control (WT) proteins.

FIG. **6**A shows microscopic images of Seldeg activity in the presence of target antigen-specific antibodies, with microscopic images of representative lysosomes cropped, expanded, and presented in the top right-corner insets. For FIG. **6**A, HMEC-1 cells were pre-pulsed with Alexa 555-labeled Dextran for 2 hours and washed, and then pulsed with 100 nM Alexa 647-labeled 8-18C5 (MOG-specific) in complex with 400 nM MOG-Seldeg or MOG-WT (as indicated) for 30 minutes, followed by an 8 hour chase and then washed, fixed and imaged. To generate the microscopic images of FIG. **6**B, HMEC-1 cells were pre-pulsed with Alexa 555-labeled Dextran for 2 hours and washed, and then pulsed with either 100 nM Alexa 647-labeled TZB or 8-18C5 antibodies, and 400 nM MOG-Seldeg or HER2-Seldeg (as indicated) for 30 minutes followed by an 8 hour chase, and then washed, fixed and imaged. For each overlay image (shown in the right column), GFP, Alexa 555 and Alexa 647 are pseudo-colored green, red and blue, respectively Bars in each of the microscopic images are 5 μm, and bars in each of the microscopic image insets are 0.25 μm Notably, FIG. **6**B shows that the cells do not accumulate TZB and 8-18C5 in lysosomes in the presence of MOG-Seldeg or HER2-Seldeg, respectively, which indicates the antigen specificity of their effects.

Example 7—Ability of Seldegs that Target Phosphatidylserine to Efficiently Internalize Target Antigen-Specific Antibodies into Cells

FIG. **7** shows that MOG-Seldeg-PS efficiently internalizes MOG-specific antibodies (chimeric 8-18C5) into endothelial cells and macrophages and uptake is dependent on PS-binding Endothelial cells (2H11) or macrophages (RAW264.7) that expose PS were incubated with 10 nM Alexa 647-labeled chimeric 8-18C5 mixed with 20 nM MOG-Seldeg-PS, MOG-Seldeg-PS(DN) or Fc-Syt1 (no MOG) for 2 hours Mean fluorescence intensities (MFI) of Alexa 647-labeled chimeric 8-18C5 (made by fusing the variable domains of the mouse antibody, 8-18C5, to the constant regions of human IgG1, Cκ, using methods well

known to those skilled in the art) for triplicate samples were determined by flow cytometry.

This exemplary PS-binding Seldeg is calcium-dependent and therefore dissociates in endosomes where the calcium concentration is much lower. Not all PS-targeting Seldegs are expected to be calcium-dependent, but some, also such as those comprising annexin V will have this property, as would be understood by skilled persons. In addition, several antibodies can bind to beta-2 glycoprotein I that can in turn bind to PS.

Example 8—Ability of Seldegs that Target the Transferrin Receptor to Efficiently Internalize Target Antigen-Specific Antibodies into Cells Expressing the Human Transferrin Receptor

A Seldeg comprising antigen (MOG) fused to an antibody that targets the transferrin receptor (MOG-Seldeg-TfR) has been generated and is shown schematically in FIG. **8**. MOG-Seldeg-TfR and control antibody, Ab-TfR (no MOG present), were purified from culture supernatants of transfected HEK-293F cells using protein G-Sepharose and standard methods MOG-Seldeg-TfR efficiently internalizes MOG-specific antibodies (chimeric 8-18C5) into endothelial (HMEC-1) cells and uptake is dependent on the presence of MOG in the Seldeg (FIG. **9**). HMEC-1 cells that express human TfR were incubated with 50 nM Alexa 647-labeled chimeric 8-18C5 (specific for MOG) mixed with 200 nM MOG-Seldeg-TfR, or TfR-specific antibody (Ab-TfR; no MOG) for 30 minutes followed by washing and no chase (30'P), or for 30 minutes followed by washing and a 60 minute chase period (30'P, 60'C). Mean fluorescence intensities (MFI) of Alexa 647-labeled 8-18C5 for triplicate samples were determined by flow cytometry (FIG. **9**).

Example 9—Ability to Seldegs that Target FcRn to Clear Background During Positron Emission Tomographic Analyses of Tumors Using Radiolabeled Antibodies

Fcmale BALB/c SCID mice were implanted in the mammary fat pad (0.5×10^6 cells/mouse; cells were suspended in RPM1-1640/Matrigel prior to injection) with the HER2-positive breast cancer cell line, HCC1954. 6-7 days later, mice were injected with 124-I labeled TZB (60 μg/mouse) and analyzed using positron emission tomography (PET) 22 hours later Mice were injected with a molar equivalent of HER2-Seldeg (51 μg/mouse) or, as controls, MOG-Seldeg (31 μg/mouse) or PBS vehicle (n=3 mice/group). Mice were analyzed using PET 4 hours following injection of the Seldegs or PBS. Imaging of mice was carried out using a Siemens Inveon PET-computed tomography (CT) Multimodality System.

To generate the date shown in FIG. **10**A, mice were imaged at 22 hours following injection of 124-I labeled TZB ('**22***h*') and at 4.5-5 hours post-injection ('**4.5***h* clearing') of HER2-Seldeg, MOG-Seldeg or PBS. PET and CT images were co-registered in the AMIDE software package. FIG. **10**B provides graphs of contrast measures for radiolabel intensity for 22 hours post-injection of 124-I labeled TZB and 4.5-5 hours post-injection of HER2-Seldeg, MOG-Seldeg or PBS. To determine contrast measures, two regions of interest were identified in the thoracic region (background) and tumor. The mean values (n=3 mice/group) for the ratios of mean intensity in the tumor to mean intensity in the thoracic regions are plotted. Error bars indicate standard errors. Statistically significant differences ($p<0.05$) between mice treated with HER2-Seldeg vs. MOG-Seldeg or PBS are shown. The data show that delivery of HER2-Seldeg reduces the background in the thoracic region of the mice.

Example 10 DNA and Proteins Sequences of Exemplary Seldegs and Controls and Variants Thereof Having Mutations Such as Knobs-into-Holes Mutations, Arginine Mutations and Electrostatic Steering Mutations

Table 1 shows DNA sequences of polynucleotides encoding exemplary proteins described herein, and Table 2 shows amino acid sequences of exemplary proteins encoded by the polynucleotides shown in Table 1, wherein the DNA sequence of SEQ ID NO: 1 encodes the protein of SEQ ID NO: 2, the DNA sequence of SEQ ID NO: 3 encodes the protein of SEQ ID NO: 4, the DNA sequence of SEQ ID NO: 5 encodes the protein of SEQ ID NO: 6, the DNA sequence of SEQ ID NO: 7 encodes the protein of SEQ ID NO: 8, the DNA sequence of SEQ ID NO: 9 encodes the protein of SEQ ID NO: 10, the DNA sequence of SEQ ID NO: 11 encodes the protein of SEQ ID NO: 12, the DNA sequence of SEQ ID NO: 13 encodes the protein of SEQ ID NO: 14, the DNA sequence of SEQ ID NO: 15 encodes the protein of SEQ ID NO: 16, the DNA sequence of SEQ ID NO: 17 encodes the protein of SEQ ID NO: 18, the DNA sequence of SEQ ID NO: 19 encodes the protein of SEQ ID NO: 20, the DNA sequence of SEQ ID NO: 21 encodes the protein of SEQ ID NO: 22, the DNA sequence of SEQ ID NO: 23 encodes the protein of SEQ ID NO: 24, the DNA sequence of SEQ ID NO: 25 encodes the protein of SEQ ID NO: 26, the DNA sequence of SEQ ID NO: 27 encodes the protein of SEQ ID NO: 28, the DNA sequence of SEQ ID NO: 29 encodes the protein of SEQ ID NO: 30, the DNA sequence of SEQ ID NO: 31 encodes the protein of SEQ ID NO: 32, the DNA sequence of SEQ ID NO: 33 encodes the protein of SEQ ID NO: 34.

TABLE 1

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
MOG-Seldeg with MST-HN, knobs-into-holes and arginine mutations	GGACAATTCAGAGTGATAGGACCAGGGTATCCCATCCGG GCTTTAGTTGGGGATGAAGCAGAGCTGCCGTGCCGCATC TCTCCTGGGAAAAATGCCACGGGCATGGAGGTGGGTTGG TACCGTTCTCCCTTCTCAAGAGTGGTTCACCTCTACCGAA ATGGCAAGGACCAAGATGCAGAGCAAGCACCTGAATACC GGGGACGCACAGAGCTTCTGAAAGAGACTATCAGTGAGG GAAAGGTTACCCTTAGGATTCAGAACGTGAGATTCTCAG	1

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
	ATGAAGGAGGCTACACCTGCTTCTTCAGAGACCACTCTTA CCAAGAAGAGGCAGCAATGGAGTTGAAAGTGGAAGATG GAGGCGGTGGATCAGTTGAGCCCAAATCTTCTGACAAAA CTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGA GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA CACCCTCTACATCACTCGGGAACCTGAGGTCACATGCGTG GTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC AACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGT GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC GCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG GGCAGCCCCGAGAACCACAGGTGACCACCCTGCCCCCAT CCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGG AGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG ACCTTCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCT CTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCTGTGATGCATGAGGCTCTG AAATTCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG GTAAA	
HER2-Seldeg with MST-HN, knobs-into-holes and arginine mutations	ACCCAAGTGTGCACCGGCACAGACATGAAGCTGCGGCTC CCTGCCAGTCCCGAGACCCACCTGGACATGCTCCGCCAC CTCTACCAGGGCTGCCAGGTGGTGCAGGGAAACCTGGAA CTCACCTACCTGCCCACCAATGCCAGCCTGTCCTTCCTGC AGGATATCCAGGAGGTGCAGGGCTACGTGCTCATCGCTC ACAACCAAGTGAGGCAGGTCCCACTGCAGAGGCTGCGGA TTGTGCGAGGCACCCAGCTCTTTGAGGACAACTATGCCCT GGCCGTGCTAGACAATGGAGACCCGCTGAACAATACCAC CCCTGTCACAGGGGCCTCCCCAGGAGGCCTGCGGGAGCT GCAGCTTCGAAGCCTCACAGAGATCTTGAAAGGAGGGGT CTTGATCCAGCGGAACCCCCAGCTCTGCTACCAGGACAC GATTTTGTGGAAGGACATCTTCCACAAGAACAACCAGCT GGCTCTCACACTGATAGACACCAACCGCTCTCGGGCCTGC CACCCCTGTTCTCCGATGTGTAAGGGCTCCCGCTGCTGGG GAGAGAGTTCTGAGGATTGTCAGAGCCTGACGCGCACTG TCTGTGCCGGTGGCTGTGCCCGCTGCAAGGGGCCACTGCC CACTGACTGCTGCCATGAGCAGTGTGCTGCCGGCTGCAC GGGCCCCAAGCACTCTGACTGCCTGGCCTGCCTCCACTTC AACCACAGTGGCATCTGTGAGCTGCACTGCCCAGCCCTG GTCACCTACAACACAGACACGTTTGAGTCCATGCCCAATC CCGAGGGCCGGTATACATTCGGCGCCAGCTGTGTGACTG CCTGTCCCTACAACTACCTTTCTACGGACGTGGGATCCTG CACCCTCGTCTGCCCCCTGCACAACCAAGAGGTGACAGC AGAGGATGGAACACAGCGGTGTGAGAAGTGCAGCAAGC CCTGTGCCCGAGTGTGCTATGGTCTGGGCATGGAGCACTT GCGAGAGGTGAGGGCAGTTACCAGTGCCAATATCCAGGA GTTTGCTGGCTGCAAGAAGATCTTTGGGAGCCTGGCATTT CTGCCGGAGAGCTTTGATGGGGACCCAGCCTCCAACACT GCCCCGCTCCAGCCAGAGCAGCTCCAAGTGTTTGAGACT CTGGAAGAGATCACAGGTTACCTATACATCTCAGCATGG CCGGACAGCCTGCCTGACCTCAGCGTCTTCCAGAACCTGC AAGTAATCCGGGGACGAATTCTGCACAATGGCGCCTACT CGCTGACCCTGCAAGGGCTGGGCATCAGCTGGCTGGGGC TGCGCTCACTGAGGGAACTGGGCAGTGGACTGGCCCTCA TCCACCATAACACCCACCTCTGCTTCGTGCACACGGTGCC CTGGGACCAGCTCTTTCGGAACCCGCACCAAGCTCTGCTC CACACTGCCAACCGGCCAGAGGACGAGTGTGTGGGCGAG GGCCTGGCCTGCCACCAGCTGTGCGCCCGAGGGCACTGC TGGGGTCCAGGGCCCACCCAGTGTGTCAACTGCAGCCAG TTCCTTCGGGGCCAGGAGTGCGTGGAGGAATGCCGAGTA CTGCAGGGGCTCCCCAGGGAGTATGTGAATGCCAGGCAC TGTTTGCCGTGCCACCCTGAGTGTCAGCCCCAGAATGGCT CAGTGACCTGTTTTGGACCGGAGGCTGACCAGTGTGTGG CCTGTGCCCACTATAAGGACCCTCCCTTCTGCGTGGCCCG CTGCCCCAGCGGTGTGAAACCTGACCTCTCCTACATGCCC ATCTGGAAGTTTCCAGATGAGGAGGGCGCATGCCAGCCT TGCCCCATCAACTGCACCCACTCCTGTGTGGACCTGGATG ACAAGGGCTGCCCCGCCGAGCAGAGAGCCAGCCCTCTGA CGATTGAAGGCCGCATGGATCCCAAATCTTCTGACAAAA CTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGA GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA CACCCTCTACATCACTCGGGAACCTGAGGTCACATGCGTG	3

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
	GTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC AACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGT GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC GCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG GGCAGCCCCGAGAACCACAGGTGACCACCCTGCCCCCAT CCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGG AGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG ACCTTCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCT CTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCTGTGATGCATGAGGCTCTG AAATTCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCTG GTAAA	
Fc with MST-HN, knobs-into-holes and arginine mutations	GTTGAGCCCAAATCTTCTGACAAAACTCACACATGCCCAC CGTGCCCAGCACCTGAACTCCTGAGGGGACCGTCAGTCTT CCTCTTCCCCCCAAAACCCAAGGACACCCTCTACATCACT CGGGAACCTGAGGTCACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA GGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCT CACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCGCCCAGCCCCCAT CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA ACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCT GACCAAGAACCAGGTCCACCTGACCTGCCTGGTCAAAGG CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT GCTGGACTCCGACGGCTCCTTCGCCCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGAAATTCCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	5
MOG-Seldeg-PS with knobs-into-holes and arginine mutations	GGACAATTCAGAGTGATAGGACCAGGGTATCCCATCCGG GCTTTAGTTGGGGATGAAGCAGAGCTGCCGTGCCGCATC TCTCCTGGGAAAAATGCCACGGGCATGGAGGTGGGTTGG TACCGTTCTCCCTTCTCAAGAGTGGTTCACCTCTACCGAA ATGGCAAGGACCAAGATGCAGAGCAAGCACCTGAATACC GGGGACGCACAGAGCTTCTGAAAGAGACTATCAGTGAGG GAAAGGTTACCCTTAGGATTCAGAACGTGAGATTCTCAG ATGAAGGAGGCTACACCTGCTTCTTCAGAGACCACTCTTA CCAAGAAGAGGCAGCAATGGAGTTGAAAGTGGAAGATG GAGGCGGTGGATCAGTTGAGCCCAAATCTTCTGACAAAA CTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGA GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA CACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTG GTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC AACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGT GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC GCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG GGCAGCCCCGAGAACCACAGGTGACCACCCTGCCCCCAT CCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGG AGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG ACCTTCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCT CTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCTGTGATGCATGAGGCTCTG CATAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG GTAAAGGAGGCGGTGGATCAGAGAAACTGGGAAAACTTC AGTATTCACTGGATTATGATTTCCAAAATAACCAGCTGCT GGTAGGGATCATTCAGGCTGCCGAACTGCCCGCCTTGGA CATGGGGGGCACATCTGATCCTTACGTGAAAGTGTTTCTG CTACCTGATAAGAAGAAGAAATTTGAGACAAAAGTCCAC CGAAAAACCCTTAATCCTGTCTTCAATGAGCAATTTACTT TCAAGGTACCATACTCGGAATTGGGTGGCAAAACCCTAG TGATGGCTGTATATGATTTTGATCGTTTCTCTAAGCATGA CATCATTGGAGAATTTAAAGTCCCTATGAACACAGTGGA TTTTGGCCATGTAACTGAGGAATGGCGTGACCTGCAAAG TGCT	7

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
Fc-Syt1 with knobs-into-holes and arginine mutations	GTTGAGCCCAAATCTTCTGACAAAACTCACACATGCCCAC CGTGCCCAGCACCTGAACTCCTGAGGGGACCGTCAGTCTT CCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA GGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCT CACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCGCCCAGCCCCCAT CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA ACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCT GACCAAGAACCAGGTCCACCTGACCTGCCTGGTCAAAGG CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT GCTGGACTCCGACGGCTCCTTCGCCCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGAGGCG GTGGATCAGAGAAACTGGGAAAACTTCAGTATTCACTGG ATTATGATTTCCAAAATAACCAGCTGCTGGTAGGGATCAT TCAGGCTGCCGAACTGCCCGCCTTGGACATGGGGGGCAC ATCTGATCCTTACGTGAAAGTGTTTCTGCTACCTGATAAG AAGAAGAAATTTGAGACAAAAGTCCACCGAAAAACCCTT AATCCTGTCTTCAATGAGCAATTTACTTTCAAGGTACCAT ACTCGGAATTGGGTGGCAAAACCCTAGTGATGGCTGTAT ATGATTTTGATCGTTTCTCTAAGCATGACATCATTGGAGA ATTTAAAGTCCCTATGAACACAGTGGATTTTGGCCATGTA ACTGAGGAATGGCGTGACCTGCAAAGTGCT	9
MOG-Seldeg-PS with knobs-into-holes, electrostatic steering and arginine mutations	GGACAATTCAGAGTGATAGGACCAGGGTATCCCATCCGG GCTTTAGTTGGGGATGAAGCAGAGCTGCCGTGCCGCATC TCTCCTGGGAAAAATGCCACGGGCATGGAGGTGGGTTGG TACCGTTCTCCCTTCTCAAGAGTGGTTCACCTCTACCGAA ATGGCAAGGACCAAGATGCAGAGCAAGCACCTGAATACC GGGGACGCACAGAGCTTCTGAAAGAGACTATCAGTGAGG GAAAGGTTACCCTTAGGATTCAGAACGTGAGATTCTCAG ATGAAGGAGGCTACACCTGCTTCTTCAGAGACCACTCTTA CCAAGAAGAGGCAGCAATGGAGTTGAAAGTGGAAGATG GAGGCGGTGGATCAGTTGAGCCCAAATCTTCTGACAAAA CTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGA GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA CACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTG GTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC AACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGT GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC GCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG GGCAGCCCCGAGAACCACAGGTGACCACCCTGCCCCCAT CCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGG AGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACGAC ACCTTCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCT CTACAGCGACCTCACCGTGGACAAGAGCAGGTGGCAGCA GGGGAACGTCTTCTCATGCTCTGTGATGCATGAGGCTCTG CATAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG GTAAAGGAGGCGGTGGATCAGAGAAACTGGGAAAACTTC AGTATTCACTGGATTATGATTTCCAAAATAACCAGCTGCT GGTAGGGATCATTCAGGCTGCCGAACTGCCCGCCTTGGA CATGGGGGGCACATCTGATCCTTACGTGAAAGTGTTTCTG CTACCTGATAAGAAGAAGAAATTTGAGACAAAAGTCCAC CGAAAAACCCTTAATCCTGTCTTCAATGAGCAATTTACTT TCAAGGTACCATACTCGGAATTGGGTGGCAAAACCCTAG TGATGGCTGTATATGATTTTGATCGTTTCTCTAAGCATGA CATCATTGGAGAATTTAAAGTCCCTATGAACACAGTGGA TTTTGGCCATGTAACTGAGGAATGGCGTGACCTGCAAAG TGCT	11

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
Fc-Syt1 with knobs-into-holes, electrostatic steering and arginine mutations	GTTGAGCCCAAATCTTCTGACAAAACTCACACATGCCCAC CGTGCCCAGCACCTGAACTCCTGAGGGGACCGTCAGTCTT CCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA GGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCT CACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCGCCCAGCCCCCAT CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA ACCACAGGTGTACACCCTGCCCCCATCCCGGGATAAGCT GACCAAGAACCAGGTCCACCTGACCTGCCTGGTCAAAGG CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT GCTGAAGTCCGACGGCTCCTTCGCCCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGAGGCG GTGGATCAGAGAAACTGGGAAAACTTCAGTATTCACTGG ATTATGATTTCCAAAATAACCAGCTGCTGGTAGGGATCAT TCAGGCTGCCGAACTGCCCGCCTTGGACATGGGGGGCAC ATCTGATCCTTACGTGAAAGTGTTTCTGCTACCTGATAAG AAGAAGAAATTTGAGACAAAAGTCCACCGAAAAACCCTT AATCCTGTCTTCAATGAGCAATTTACTTTCAAGGTACCAT ACTCGGAATTGGGTGGCAAAACCCTAGTGATGGCTGTAT ATGATTTTGATCGTTTCTCTAAGCATGACATCATTGGAGA ATTTAAAGTCCCTATGAACACAGTGGATTTTGGCCATGTA ACTGAGGAATGGCGTGACCTGCAAAGTGCT	13
MOG-Seldeg-TfR with knobs-into-holes mutations	GAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAG CCCGGCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCCGGCT ACACCTTCACCTCCTACTGGATGCACTGGGTGCGGCAGGC CCCCGGCCAGCGGCTGGAGTGGATCGGCGAGATCAACCC CACCAACGGCCGGACCAACTACATCGAGAAGTTCAAGTC CCGGGCCACCCTGACCGTGGACAAGTCCGCCTCCACCGC CTACATGGAGCTGTCCTCCCTGCGGTCCGAGGACACCGCC GTGTACTACTGCGCCCGGGGCACCCGGGCCTACCACTACT GGGGCCAGGGCACCATGGTGACCGTGTCCTCCGCCTCCA CCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAA GAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGT CAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAA CTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGC TGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG GTGACTGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTG GACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCAC ACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGT GGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTG GTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGT CAGCGTCCTTACCGTCCTGCACCAGGACTGGCTGAATGGC AAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA GCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG CCCCGAGAACCACAGGTGACCACCCTGCCCCCATCCCGG GATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTG GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCTTC CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACA GCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACA ACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AAGGAGGCGGTGGATCAGGACAATTCAGAGTGATAGGAC CAGGGTATCCCATCCGGGCTTTAGTTGGGGATGAAGCAG AGCTGCCGTGCCGCATCTCTCCTGGGAAAAATGCCACGG GCATGGAGGTGGGTTGGTACCGTTCTCCCTTCTCAAGAGT GGTTCACCTCTACCGAAATGGCAAGGACCAAGATGCAGA GCAAGCACCTGAATACCGGGGACGCACAGAGCTTCTGAA AGAGACTATCAGTGAGGGAAAGGTTACCCTTAGGATTCA GAACGTGAGATTCTCAGATGAAGGAGGCTACACCTGCTT CTTCAGAGACCACTCTTACCAAGAAGAGGCAGCAATGGA GTTGAAAGTGGAAGAT	15

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
TfR Ab with knobs-into-holes mutations	GAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAG CCCGGCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCCGGCT ACACCTTCACCTCCTACTGGATGCACTGGGTGCGGCAGGC CCCCGGCCAGCGGCTGGAGTGGATCGGCGAGATCAACCC CACCAACGGCCGGACCAACTACATCGAGAAGTTCAAGTC CCGGGCCACCCTGACCGTGGACAAGTCCGCCTCCACCGC CTACATGGAGCTGTCCTCCCTGCGGTCCGAGGACACCGCC GTGTACTACTGCGCCCGGGGCACCCGGGCCTACCACTACT GGGGCCAGGGCACCATGGTGACCGTGTCCTCCGCCTCCA CCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAA GAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGT CAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAA CTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGC TGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG GTGACTGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTG GACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCAC ACATGCCCACCGTGCCCAGCACCTGAACTCCTGGGGGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGT GGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTG GTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGT CAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCC AGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA GCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCG GGATGAGCTGACCAAGAACCAGGTCCACCTGACCTGCCT GGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCA CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCGCCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGG GGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT AAA	17
TfR Ab LC	GACATCCAGATGACCCAGTCCCCCTCCTCCCTGTCCGCCT CCGTGGGCGACCGGGTGACCATCACCTGCCGGGCCTCCG ACAACCTGTACTCCAACCTGGCCTGGTACCAGCAGAAGC CCGGCAAGTCCCCCAAGCTGCTGGTGTACGACGCCACCA ACCTGGCCGACGGCGTGCCCTCCCGGTTCTCCGGCTCCGG CTCCGGCACCGACTACACCCTGACCATCTCCTCCCTGCAG CCCGAGGACTTCGCCACCTACTACTGCCAGCACTTCTGGG GCACCCCCCTGACCTTCGGCCAGGGCACCAAGGTGGAGA TCAAGACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCC ATCTGATGAGCAGTTGAAATCTGGAACTGCCTCTGTTGTG TGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTA CAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCAC CTACAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGA CTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCA TCAGGGCCTGAGTTCGCCCGTCACAAAGAGCTTCAACAG GGGAGAGTGT	19
MOG-Seldeg-TfR with knobs-into-holes and arginine mutations	GAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAG CCCGGCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCCGGCT ACACCTTCACCTCCTACTGGATGCACTGGGTGCGGCAGGC CCCCGGCCAGCGGCTGGAGTGGATCGGCGAGATCAACCC CACCAACGGCCGGACCAACTACATCGAGAAGTTCAAGTC CCGGGCCACCCTGACCGTGGACAAGTCCGCCTCCACCGC CTACATGGAGCTGTCCTCCCTGCGGTCCGAGGACACCGCC GTGTACTACTGCGCCCGGGGCACCCGGGCCTACCACTACT GGGGCCAGGGCACCATGGTGACCGTGTCCTCCGCCTCCA CCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAA GAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGT CAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAA CTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGC TGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG GTGACTGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTG GACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCAC ACATGCCCACCGTGCCCAGCACCTGAACTCCTGAGGGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC	21

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
	TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGT GGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTG GTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGT CAGCGTCCTTACCGTCCTGCACCAGGACTGGCTGAATGGC AAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCGCCCA GCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAG CCCCGAGAACCACAGGTGACCACCCTGCCCCCATCCCGG GATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTG GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGG GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCTTC CCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACA GCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGG AACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACA ACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTA AAGGAGGCGGTGGATCAGGACAATTCAGAGTGATAGGAC CAGGGTATCCCATCCGGGCTTTAGTTGGGGATGAAGCAG AGCTGCCGTGCCGCATCTCTCCTGGGAAAAATGCCACGG GCATGGAGGTGGGTTGGTACCGTTCTCCCTTCTCAAGAGT GGTTCACCTCTACCGAAATGGCAAGGACCAAGATGCAGA GCAAGCACCTGAATACCGGGGACGCACAGAGCTTCTGAA AGAGACTATCAGTGAGGGAAAGGTTACCCTTAGGATTCA GAACGTGAGATTCTCAGATGAAGGAGGCTACACCTGCTT CTTCAGAGACCACTCTTACCAAGAAGAGGCAGCAATGGA GTTGAAAGTGGAAGAT	
TfR Ab with knobs-into-holes and arginine mutations	GAGGTGCAGCTGGTGCAGTCCGGCGCCGAGGTGAAGAAG CCCGGCGCCTCCGTGAAGGTGTCCTGCAAGGCCTCCGGCT ACACCTTCACCTCCTACTGGATGCACTGGGTGCGGCAGGC CCCCGGCCAGCGGCTGGAGTGGATCGGCGAGATCAACCC CACCAACGGCCGGACCAACTACATCGAGAAGTTCAAGTC CCGGGCCACCCTGACCGTGGACAAGTCCGCCTCCACCGC CTACATGGAGCTGTCCTCCCTGCGGTCCGAGGACACCGCC GTGTACTACTGCGCCCGGGGCACCCGGGCCTACCACTACT GGGGCCAGGGCACCATGGTGACCGTGTCCTCCGCCTCCA CCAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAA GAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGT CAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAA CTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGC TGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTG GTGACTGTGCCCTCCAGCAGCTTGGGCACCCAGACCTAC ATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTG GACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCAC ACATGCCCACCGTGCCCAGCACCTGAACTCCTGAGGGGA CCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGT GGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTG GTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA GCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGT CAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCGCCC AGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA GCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCG GGATGAGCTGACCAAGAACCAGGTCCACCTGACCTGCCT GGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTG GGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCA CGCCTCCCGTGCTGGACTCCGACGGCTCCTTCGCCCTCTA CAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGG GGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCA CAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGT AAA	23
HER2-ECD-Fc with MST-HN and knobs-into-holes	ACCCAAGTGTGCACCGGCACAGACATGAAGCTGCGGCTC CCTGCCAGTCCCGAGACCCACCTGGACATGCTCCGCCAC CTCTACCAGGGCTGCCAGGTGGTGCAGGGAAACCTGGAA CTCACCTACCTGCCCACCAATGCCAGCCTGTCCTTCCTGC AGGATATCCAGGAGGTGCAGGGCTACGTGCTCATCGCTC ACAACCAAGTGAGGCAGGTCCCACTGCAGAGGCTGCGGA TTGTGCGAGGCACCCAGCTCTTTGAGGACAACTATGCCCT GGCCGTGCTAGACAATGGAGACCCGCTGAACAATACCAC CCCTGTCACAGGGGCCTCCCCAGGAGGCCTGCGGGAGCT GCAGCTTCGAAGCCTCACAGAGATCTTGAAAGGAGGGGT CTTGATCCAGCGGAACCCCCAGCTCTGCTACCAGGACAC GATTTTGTGGAAGGACATCTTCCACAAGAACAACCAGCT	25

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
	GGCTCTCACACTGATAGACACCAACCGCTCTCGGGCCTGC	
	CACCCCTGTTCTCCGATGTGTAAGGGCTCCCGCTGCTGGG	
	GAGAGAGTTCTGAGGATTGTCAGAGCCTGACGCGCACTG	
	TCTGTGCCGGTGGCTGTGCCCGCTGCAAGGGGCCACTGCC	
	CACTGACTGCTGCCATGAGCAGTGTGCTGCCGGCTGCAC	
	GGGCCCCAAGCACTCTGACTGCCTGGCCTGCCTCCACTTC	
	AACCACAGTGGCATCTGTGAGCTGCACTGCCCAGCCCTG	
	GTCACCTACAACACAGACACGTTTGAGTCCATGCCCAATC	
	CCGAGGGCCGGTATACATTCGGCGCCAGCTGTGTGACTG	
	CCTGTCCCTACAACTACCTTTCTACGGACGTGGGATCCTG	
	CACCCTCGTCTGCCCCCTGCACAACCAAGAGGTGACAGC	
	AGAGGATGGAACACAGCGGTGTGAGAAGTGCAGCAAGC	
	CCTGTGCCCGAGTGTGCTATGGTCTGGGCATGGAGCACTT	
	GCGAGAGGTGAGGGCAGTTACCAGTGCCAATATCCAGGA	
	GTTTGCTGGCTGCAAGAAGATCTTTGGGAGCCTGGCATTT	
	CTGCCGGAGAGCTTTGATGGGGACCCAGCCTCCAACACT	
	GCCCCGCTCCAGCCAGAGCAGCTCCAAGTGTTTGAGACT	
	CTGGAAGAGATCACAGGTTACCTATACATCTCAGCATGG	
	CCGGACAGCCTGCCTGACCTCAGCGTCTTCCAGAACCTGC	
	AAGTAATCCGGGGACGAATTCTGCACAATGGCGCCTACT	
	CGCTGACCCTGCAAGGGCTGGGCATCAGCTGGCTGGGGC	
	TGCGCTCACTGAGGGAACTGGGCAGTGGACTGGCCCTCA	
	TCCACCATAACACCCACCTCTGCTTCGTGCACACGGTGCC	
	CTGGGACCAGCTCTTTCGGAACCCGCACCAAGCTCTGCTC	
	CACACTGCCAACCGGCCAGAGGACGAGTGTGTGGGCGAG	
	GGCCTGGCCTGCCACCAGCTGTGCGCCCGAGGGCACTGC	
	TGGGGTCCAGGGCCCACCCAGTGTGTCAACTGCAGCCAG	
	TTCCTTCGGGGCCAGGAGTGCGTGGAGGAATGCCGAGTA	
	CTGCAGGGGCTCCCCAGGGAGTATGTGAATGCCAGGCAC	
	TGTTTGCCGTGCCACCCTGAGTGTCAGCCCCAGAATGGCT	
	CAGTGACCTGTTTTGGACCGGAGGCTGACCAGTGTGTGG	
	CCTGTGCCCACTATAAGGACCCTCCCTTCTGCGTGGCCCG	
	CTGCCCCAGCGGTGTGAAACCTGACCTCTCCTACATGCCC	
	ATCTGGAAGTTTCCAGATGAGGAGGGCGCATGCCAGCCT	
	TGCCCCATCAACTGCACCCACTCCTGTGTGGACCTGGATG	
	ACAAGGGCTGCCCCGCCGAGCAGAGAGCCAGCCCTCTGA	
	CGATTGAAGGCCGCATGGATCCCAAATCTTCTGACAAAA	
	CTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGG	
	GGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA	
	CACCCTCTACATCACTCGGGAACCTGAGGTCACATGCGTG	
	GTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTC	
	AACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAG	
	ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGT	
	GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGA	
	ATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCC	
	TCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAG	
	GGCAGCCCCGAGAACCACAGGTGACCACCCTGCCCCCAT	
	CCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCT	
	GCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGG	
	AGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAG	
	ACCTTCCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCT	
	CTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCA	
	GGGGAACGTCTTCTCATGCTCTGTGATGCATGAGGCTCTG	
	AAATTCCACTACACGCAGAAGAGCCTCTCCCTGTCTCCTG	
	GTAAA	
Fc with MST-HN and knobs-into-holes mutations	GTTGAGCCCAAATCTTCTGACAAAACTCACACATGCCCAC	27
	CGTGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTT	
	CCTCTTCCCCCCAAAACCCAAGGACACCCTCTACATCACT	
	CGGGAACCTGAGGTCACATGCGTGGTGGTGGACGTGAGC	
	CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGAC	
	GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA	
	GGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCT	
	CACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA	
	CAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCAT	
	CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA	
	ACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCT	
	GACCAAGAACCAGGTCCACCTGACCTGCCTGGTCAAAGG	
	CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA	
	TGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGT	
	GCTGGACTCCGACGGCTCCTTCGCCCTCTACAGCAAGCTC	
	ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC	
	TCATGCTCCGTGATGCATGAGGCTCTGAAATTCCACTACA	
	CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
PSMA-Seldeg with MST-HN, knobs-into-holes and arginine mutations	GTTGAGCCCAAATCTTCTGACAAAACTCACACATGCCCAC CGTGCCCAGCACCTGAACTCCTGAGGGGACCGTCAGTCTT CCTCTTCCCCCCAAAACCCAAGGACACCCTCTACATCACT CGGGAACCTGAGGTCACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGAC GGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGA GGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCT CACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTA CAAGTGCAAGGTCTCCAACAAAGCCCGCCCAGCCCCCAT CGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGA ACCACAGGTGACCACCCTGCCCCCATCCCGGGATGAGCT GACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGG CTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAA TGGGCAGCCGGAGAACAACTACAAGACCTTCCCTCCCGT GCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTC ACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTC TCATGCTCTGTGATGCATGAGGCTCTGAAATTCCACTACA CGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAGGAGGCG GTGGATCAAAATCCTCCAATGAAGCTACTAACATTACTCC AAAGCATAATATGAAAGCATTTTTGGATGAATTGAAAGC TGAGAACATCAAGAAGTTCTTATATAATTTTACACAGATA CCACATTTAGCAGGAACAGAACAAAACTTTCAGCTTGCA AAGCAAATTCAATCCCAGTGGAAAGAATTTGGCCTGGAT TCTGTTGAGCTAGCACATTATGATGTCCTGTTGTCCTACC CAAATAAGACTCATCCCAACTACATCTCAATAATTAATGA AGATGGAAATGAGATTTTCAACACATCATTATTTGAACCA CCTCCTCCAGGATATGAAAATGTTTCGGATATTGTACCAC CTTTCAGTGCTTTCTCTCCTCAAGGAATGCCAGAGGGCGA TCTAGTGTATGTTAACTATGCACGAACTGAAGACTTCTTT AAATTGGAACGGGACATGAAAATCAATTGCTCTGGGAAA ATTGTAATTGCCAGATATGGGAAAGTTTTCAGAGGAAAT AAGGTTAAAAATGCCCAGCTGGCAGGGGCCAAAGGAGTC ATTCTCTACTCCGACCCTGCTGACTACTTTGCTCCTGGGG TGAAGTCCTATCCAGATGGTTGGAATCTTCCTGGAGGTGG TGTCCAGCGTGGAAATATCCTAAATCTGAATGGTGCAGG AGACCCTCTCACACCAGGTTACCCAGCAAATGAATATGC TTATAGGCGTGGAATTGCAGAGGCTGTTGGTCTTCCAAGT ATTCCTGTTCATCCAATTGGATACTATGATGCACAGAAGC TCCTAGAAAAAATGGGTGGCTCAGCACCACCAGATAGCA GCTGGAGAGGAAGTCTCAAAGTGCCCTACAATGTTGGAC CTGGCTTTACTGGAAACTTTTCTACACAAAAAGTCAAGAT GCACATCCACTCTACCAATGAAGTGACAAGAATTTACAA TGTGATAGGTACTCTCAGAGGAGCAGTGGAACCAGACAG ATATGTCATTCTGGGAGGTCACCGGGACTCATGGGTGTTT GGTGGTATTGACCCTCAGAGTGGAGCAGCTGTTGTTCATG AAATTGTGAGGAGCTTTGGAACACTGAAAAAGGAAGGGT GGAGACCTAGAAGAACAATTTTGTTTGCAAGCTGGGATG CAGAAGAATTTGGTCTTCTTGGTTCTACTGAGTGGGCAGA GGAGAATTCAAGACTCCTTCAAGAGCGTGGCGTGGCTTA TATTAATGCTGACTCATCTATAGAAGGAAACTACACTCTG AGAGTTGATTGTACACCGCTGATGTACAGCTTGGTACACA ACCTAACAAAAGAGCTGAAAAGCCCTGATGAAGGCTTTG AAGGCAAATCTCTTTATGAAAGTTGGACTAAAAAAAGTC CTTCCCCAGAGTTCAGTGGCATGCCCAGGATAAGCAAAT TGGGATCTGGAAATGATTTTGAGGTGTTCTTCCAACGACT TGGAATTGCTTCAGGCAGAGCACGGTATACTAAAAATTG GGAAACAAACAAATTCAGCGGCTATCCACTGTATCACAG TGTCTATGAAACATATGAGTTGGTGGAAAAGTTTTATGAT CCAATGTTTAAATATCACCTCACTGTGGCCCAGGTTCGAG GAGGGATGGTGTTTGAGCTAGCCAATTCCATAGTGCTCCC TTTTGATTGTCGAGATTATGCTGTAGTTTTAAGAAAGTAT GCTGACAAAATCTACAGTATTTCTATGAAACATCCACAG GAAATGAAGACATACAGTGTATCATTTGATTCACTTTTTT CTGCAGTAAAGAATTTTACAGAAATTGCTTCCAAGTTCAG TGAGAGACTCCAGGACTTTGACAAAAGCAACCCAATAGT ATTAAGAATGATGAATGATCAACTCATGTTTCTGGAAAG AGCATTTATTGATCCATTAGGGTTACCAGACAGGCCTTTT TATAGGCATGTCATCTATGCTCCAAGCAGCCACAACAAG TATGCAGGGGAGTCATTCCCAGGAATTTATGATGCTCTGT TTGATATTGAAAGCAAAGTGGACCCTTCCAAGGCCTGGG GAGAAGTGAAGAGACAGATTTATGTTGCAGCCTTCACAG TGCAGGCAGCTGCAGAGACTTTGAGTGAAGTAGCC	29

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
GAD65-Seldeg with MST-HN, knobs-into-holes and arginine mutations	ATGGCATCTCCGGGCTCTGGCTTTTGGTCTTTCGGGTCGG AAGATGGCTCTGGGGATTCCGAGAATCCCGGCACAGCGC GAGCCTGGTGCCAAGTGGCTCAGAAGTTCACGGGCGGCA TCGGAAACAAACTGTGCGCCCTGCTCTACGGAGACGCCG AGAAGCCGGCGGAGAGCGGCGGGAGCCAACCCCCGCGG GCCGCCGCCCGGAAGGCCGCCTGCGCCTGCGACCAGAAG CCCTGCAGCTGCTCCAAAGTGGATGTCAACTACGCGTTTC TCCATGCAACAGACCTGCTGCCGGCGTGTGATGGAGAAA GGCCCACTTTGGCGTTTCTGCAAGATGTTATGAACATTTT ACTTCAGTATGTGGTGAAAAGTTTCGATAGATCAACCAA AGTGATTGATTTCCATTATCCTAATGAGCTTCTCCAAGAA TATAATTGGGAATTGGCAGACCAACCACAAAATTTGGAG GAAATTTTGATGCATTGCCAAACAACTCTAAAATATGCA ATTAAAACAGGGCATCCTAGATACTTCAATCAACTTTCTA CTGGTTTGGATATGGTTGGATTAGCAGCAGACTGGCTGAC ATCAACAGCAAATACTAACATGTTCACCTATGAAATTGCT CCAGTATTTGTGCTTTTGGAATATGTCACACTAAAGAAAA TGAGAGAAATCATTGGCTGGCCAGGGGGCTCTGGCGATG GGATATTTTCTCCCGGTGGCGCCATATCTAACATGTATGC CATGATGATCGCACGCTTTAAGATGTTCCCAGAAGTCAA GGAGAAAGGAATGGCTGCTCTTCCCAGGCTCATTGCCTTC ACGTCTGAACATAGTCATTTTTCTCTCAAGAAGGGAGCTG CAGCCTTAGGGATTGGAACAGACAGCGTGATTCTGATTA AATGTGATGAGAGAGGGAAAATGATTCCATCTGATCTTG AAAGAAGGATTCTTGAAGCCAAACAGAAAGGGTTTGTTC CTTTCCTCGTGAGTGCCACAGCTGGAACCACCGTGTACGG AGCATTTGACCCCCTCTTAGCTGTCGCTGACATTTGCAAA AAGTATAAGATCTGGATGCATGTGGATGCAGCTTGGGGT GGGGGATTACTGATGTCCCGAAAACACAAGTGGAAACTG AGTGGCGTGGAGAGGGCCAACTCTGTGACGTGGAATCCA CACAAGATGATGGGAGTCCCTTTGCAGTGCTCTGCTCTCC TGGTTAGAGAAGAGGGATTGATGCAGAATTGCAACCAAA TGCATGCCTCCTACCTCTTTCAGCAAGATAAACATTATGA CCTGTCCTATGACACTGGAGACAAGGCCTTACAGTGCGG ACGCCACGTTGATGTTTTTAAACTATGGCTGATGTGGAGG GCAAAGGGGACTACCGGGTTTGAAGCGCATGTTGATAAA TGTTTGGAGTTGGCAGAGTATTTATACAACATCATAAAAA ACCGAGAAGGATATGAGATGGTGTTTGATGGGAAGCCTC AGCACACAAATGTCTGCTTCTGGTACATTCCTCCAAGCTT GCGTACTCTGGAAGACAATGAAGAGAGAATGAGTCGCCT CTCGAAGGTGGCTCCAGTGATTAAAGCCAGAATGATGGA GTATGGAACCACAATGGTCAGCTACCAACCCTTGGGAGA CAAGGTCAATTTCTTCCGCATGGTCATCTCAAACCCAGCG GCAACTCACCAAGACATTGACTTCCTGATTGAAGAAATA GAACGCCTTGGACAAGATTTAGGAGGCGGTGGATCAGTT GAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCG TGCCCAGCACCTGAACTCCTGAGGGGACCGTCAGTCTTCC TCTTCCCCCCAAAACCCAAGGACACCCTCTACATCACTCG GGAACCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCA CGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGG CGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG AGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCA CCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACA AGTGCAAGGTCTCCAACAAAGCCCGCCCAGCCCCCATCG AGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC CACAGGTGACCACCCTGCCCCCATCCCGGGATGAGCTGA CCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCT TCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATG GGCAGCCGGAGAACAACTACAAGACCTTCCCTCCCGTGC TGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCAC CGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTC ATGCTCTGTGATGCATGAGGCTCTGAAATTCCACTACACG CAGAAGAGCCTCTCCCTGTCTCCGGGTAAA	31
AQP4-Seldeg with MST-HN, knobs-into-holes and arginine mutations	ATGAGTGACAGACCCACAGCAAGGCGGTGGGGTAAGTGT GGACCTTTGTGTACCAGAGAGAACATCATGGTGGCTTTCA AAGGGGTCTGGACTCAAGCTTTCTGGAAAGCAGTCACAG CGGAATTTCTGGCCATGCTTATTTTTGTTCTCCTCAGCCTG GGATCCACCATCAACTGGGGTGGAACAGAAAAGCCTTTA CCGGTCGACATGGTTCTCATCTCCCTTTGCTTTGGACTCA GCATTGCAACCATGGTGCAGTGCTTTGGCCATATCAGCGG TGGCCACATCAACCCTGCAGTGACTGTGGCCATGGTGTGC ACCAGGAAGATCAGCATCGCCAAGTCTGTCTTCTACATCG CAGCCCAGTGCCTGGGGGCCATCATTGGAGCAGGAATCC	33

TABLE 1-continued

DNA sequences of polynucleotides encoding exemplary proteins.

Polynucleotide encoding protein	DNA sequence	SEQ ID NO:
	TCTATCTGGTCACACCTCCCAGTGTGGTGGGAGGCCTGGG	
	AGTCACCATGGTTCATGGAAATCTTACCGCTGGTCATGGT	
	CTCCTGGTTGAGTTGATAATCACATTTCAATTGGTGTTTA	
	CTATCTTTGCCAGCTGTGATTCCAAACGGACTGATGTCAC	
	TGGCTCAATAGCTTTAGCAATTGGATTTTCTGTTGCAATT	
	GGACATTTATTTGCAATCAATTATACTGGTGCCAGCATGA	
	ATCCCGCCCGATCCTTTGGACCTGCAGTTATCATGGGAAA	
	TTGGGAAAACCATTGGATATATTGGGTTGGGCCCATCATA	
	GGAGCTGTCCTCGCTGGTGGCCTTTATGAGTATGTCTTCT	
	GTCCAGATGTTGAATTCAAACGTCGTTTTAAAGAAGCCTT	
	CAGCAAAGCTGCCCAGCAAACAAAAGGAAGCTACATGG	
	AGGTGGAGGACAACAGGAGTCAGGTAGAGACGGATGAC	
	CTGATTCTAAAACCTGGAGTGGTGCATGTGATTGACGTTG	
	ACCGGGGAGAGGAGAAGAAGGGGAAAGACCAATCTGGA	
	GAGGTATTGTCTTCAGTAGGAGGCGGTGGATCAGTTGAG	
	CCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCC	
	CAGCACCTGAACTCCTGAGGGGACCGTCAGTCTTCCTCTT	
	CCCCCCAAAACCCAAGGACACCCTCTACATCACTCGGGA	
	ACCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGA	
	AGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGT	
	GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGC	
	AGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCG	
	TCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGT	
	GCAAGGTCTCCAACAAAGCCCGCCCAGCCCCCATCGAGA	
	AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCAC	
	AGGTGACCACCCTGCCCCCATCCCGGGATGAGCTGACCA	
	AGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCT	
	ATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC	
	AGCCGGAGAACAACTACAAGACCTTCCCTCCCGTGCTGG	
	ACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT	
	GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATG	
	CTCTGTGATGCATGAGGCTCTGAAATTCCACTACACGCAG	
	AAGAGCCTCTCCCTGTCTCCGGGTAAA	

TABLE 2

Amino acid sequences of exemplary proteins.

Protein	Amino acid sequence	SEQ ID NO:
MOG-Seldeg with MST-HN, knobs-into-holes and arginine mutations	GQFRVIGPGYPIRALVGDEAELPCRISPGKNATGMEVGWYRS PFSRVVHLYRNGKDQDAEQAPEYRGRTELLKETISEGKVTLRI QNVRFSDEGGYTCFFRDHSYQEEAAMELKVEDGGGGSVEPK SSDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLYITREPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTISKAKGQPR EPQVTTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTFPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALKFHYTQKSLSLSPGK	2
HER2-Seldeg with MST-HN, knobs-into-holes and arginine mutations	TQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELT YLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQ LFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTEIL KGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRAC HPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTD CCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNT DTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLH NQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRAVTSA NIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETL EEITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQG LGISWLGLRSLRELGSGLALIHHNTHLCFVHTVPWDQLFRNP HQALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQCVN CSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNG SVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIW KFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTIEGRM DPKSSDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLYITREPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTISKAK GQPREPQVTTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES	4

TABLE 2-continued

Amino acid sequences of exemplary proteins.

Protein	Amino acid sequence	SEQ ID NO:
	NGQPENNYKTFPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALKFHYTQKSLSLSPGK	
Fc with MST-HN, knobs-into-holes and arginine mutations	VEPKSSDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLYITREPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVHLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFALYSKLTVDKSRWQQGNVFS CSVMHEALKFHYTQKSLSLSPGK	6
MOG-Seldeg-PS with knobs-into-holes and arginine mutations	GQFRVIGPGYPIRALVGDEAELPCRISPGKNATGMEVGWYRS PFSRVVHLYRNGKDQDAEQAPEYRGRTELLKETISEGKVTLRI QNVRFSDEGGYTCFFRDHSYQEEAAMELKVEDGGGGSVEPK SSDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTISKAKGQPR EPQVTTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTFPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKGGGGSEKLGKLQYSLDYDFQNNQ LLVGIIQAAELPALDMGGTSDPYVKVFLLPDKKKKFETKVHR KTLNPVFNEQFTFKVPYSELGGKTLVMAVYDFDRFSKHDIIGE FKVPMNTVDFGHVTEEWRDLQSA	8
Fc-Syt1 with knobs-into-holes and arginine mutations	VEPKSSDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVHLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFALYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGKGGGGSEKLGKLQYSLDYD FQNNQLLVGIIQAAELPALDMGGTSDPYVKVFLLPDKKKKFE TKVHRKTLNPVFNEQFTFKVPYSELGGKTLVMAVYDFDRFSK HDIIGEFKVPMNTVDFGHVTEEWRDLQSA	10
MOG-Seldeg-PS with knobs-into-holes, electrostatic steering and arginine mutations	GQFRVIGPGYPIRALVGDEAELPCRISPGKNATGMEVGWYRS PFSRVVHLYRNGKDQDAEQAPEYRGRTELLKETISEGKVTLRI QNVRFSDEGGYTCFFRDHSYQEEAAMELKVEDGGGGSVEPK SSDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTISKAKGQPR EPQVTTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYDTFPPVLDSDGSFFLYSDLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKGGGGSEKLGKLQYSLDYDFQNNQ LLVGIIQAAELPALDMGGTSDPYVKVFLLPDKKKKFETKVHR KTLNPVFNEQFTFKVPYSELGGKTLVMAVYDFDRFSKHDIIGE FKVPMNTVDFGHVTEEWRDLQSA	12
Fc-Syt1 with knobs-into-holes, electrostatic steering and arginine mutations	VEPKSSDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTISKAK GQPREPQVYTLPPSRDKLTKNQVHLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLKSDGSFALYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGKGGGGSEKLGKLQYSLDYD FQNNQLLVGIIQAAELPALDMGGTSDPYVKVFLLPDKKKKFE TKVHRKTLNPVFNEQFTFKVPYSELGGKTLVMAVYDFDRFSK HDIIGEFKVPMNTVDFGHVTEEWRDLQSA	14
MOG-Seldeg-TfR with knobs-into-holes mutations	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQA PGQRLEWIGEINPTNGRTNYIEKFKSRATLTVDKSASTAYMEL SSLRSEDTAVYYCARGTRAYHYWGQGTMVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVTTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTFPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGQFRVIGPGY PIRALVGDEAELPCRISPGKNATGMEVGWYRSPFSRVVHLYR NGKDQDAEQAPEYRGRTELLKETISEGKVTLRIQNVRFSDEG GYTCFFRDHSYQEEAAMELKVED	16

TABLE 2-continued

Amino acid sequences of exemplary proteins.

Protein	Amino acid sequence	SEQ ID NO:
TfR Ab with knobs-into-holes mutations	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMEIWVRQA PGQRLEWIGEINPTNGRTNYIEKFKSRATLTVDKSASTAYMEL SSLRSEDTAVYYCARGTRAYHYWGQGTMVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVHLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFALYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	18
TfR Ab LC	DIQMTQSPSSLSASVGDRVTITCRASDNLYSNLAWYQQKPGK SPKLLVYDATNLADGVPSRFSGSGSGTDYTLTISSLQPEDFAT YYCQHFWGTPLTFGQGTKVEIKTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE C	20
MOG-Seldeg-TfR with knobs-into-holes and arginine mutations	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMEIWVRQA PGQRLEWIGEINPTNGRTNYIEKFKSRATLTVDKSASTAYMEL SSLRSEDTAVYYCARGTRAYHYWGQGTMVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTI SKAKGQPREPQVTTLPPSRDELTKNQVSLTCLVKGFYPSDIAV EWESNGQPENNYKTFPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGQFRVIGPGY PIRALVGDEAELPCRISPGKNATGMEVGWYRSPFSRVVHLYR NGKDQDAEQAPEYRGRTELLKETISEGKVTLRIQNVRFSDEG GYTCFFRDHSYQEEAAMELKVED	22
TfR Ab with knobs-into-holes and arginine mutations	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYWMHWVRQA PGQRLEWIGEINPTNGRTNYIEKFKSRATLTVDKSASTAYMEL SSLRSEDTAVYYCARGTRAYHYWGQGTMVTVSSASTKGPSV FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQVHLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFALYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK	24
HER2-ECD-Fc with MST-HN and knobs-into-holes	TQVCTGTDMKLRLPASPETHLDMLRHLYQGCQVVQGNLELT YLPTNASLSFLQDIQEVQGYVLIAHNQVRQVPLQRLRIVRGTQ LFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQLRSLTEIL KGGVLIQRNPQLCYQDTILWKDIFHKNNQLALTLIDTNRSRAC HPCSPMCKGSRCWGESSEDCQSLTRTVCAGGCARCKGPLPTD CCHEQCAAGCTGPKHSDCLACLHFNHSGICELHCPALVTYNT DTFESMPNPEGRYTFGASCVTACPYNYLSTDVGSCTLVCPLH NQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRAVTSA NIQEFAGCKKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETL EEITGYLYISAWPDSLPDLSVFQNLQVIRGRILHNGAYSLTLQG LGISWLGLRSLRELGSGLALIHHNTHLCFVHTVPWDQLFRNP HQALLHTANRPEDECVGEGLACHQLCARGHCWGPGPTQCVN CSQFLRGQECVEECRVLQGLPREYVNARHCLPCHPECQPQNG SVTCFGPEADQCVACAHYKDPPFCVARCPSGVKPDLSYMPIW KFPDEEGACQPCPINCTHSCVDLDDKGCPAEQRASPLTIEGRM DPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVTTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTFPPVLDSDGSFFLYSKLTVDKSRWQQGNVFScS VMHEALKFHYTQKSLSLSPGK	26

TABLE 2-continued

Amino acid sequences of exemplary proteins.

Protein	Amino acid sequence	SEQ ID NO:
Fc with MST-HN and knobs-into-holes mutations	VEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK GQPREPQVYTLPPSRDELTKNQVHLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFALYSKLTVDKSRWQQGNVFS CSVMHEALKFHYTQKSLSLSPGK	28
PSMA-Seldeg with MST-HN, knobs-into-holes and arginine mutations	VEPKSSDKTHTCPPCPAPELLRGPSVFLFPPKPKDTLYITREPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKARPAPIEKTISKAK GQPREPQVTTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSC SVMHEALKFHYTQKSLSLSPGKGGGGSKSSNEATNITPKHNM KAFLDELKAENIKKFLYNFTQIPHLAGTEQNFQLAKQIQSQW KEFGLDSVELAHYDVLLSYPNKTHPNYISTINEDGNEIFNTSLF EPPPPGYENVSDIVPPFSAFSPQGMPEGDLVYVNYARTEDFFK LERDMKINCSGKIVIARYGKVFRGNKVKNAQLAGAKGVILYS DPADYFAPGVKSYPDGWNLPGGGVQRGNILNLNGAGDPLTP GYPANEYAYRRGIAEAVGLPSIPVHPIGYYDAQKLLEKMGGS APPDSSWRGSLKVPYNVGPGFTGNFSTQKVKMHIHSTNEVTR IYNVIGTLRGAVEPDRYVILGGHRDSWVFGGIDPQSGAAVVH EIVRSFGTLKKEGWRPRRTILFASWDAEEFGLLGSTEWAEENS RLLQERGVAYINADSSIEGNYTLRVDCTPLMYSLVHNLTKEL KSPDEGFEGKSLYESWTKKSPSPEFSGMPRISKLGSGNDFEVF FQRLGIASGRARYTKNWETNKFSGYPLYHSVYETYELVEKFY DPMFKYHLTVAQVRGGMVFELANSIVLPFDCRDYAVVLRKY ADKIYSISMKHPQEMKTYSVSFDSLFSAVKNFTEIASKFSERLQ DFDKSNPIVLRMMNDQLMFLERAFIDPLGLPDRPFYRHVIYAP SSHNKYAGESFPGIYDALFDIESKVDPSKAWGEVKRQIYVAAF TVQAAAETLSEVA	30
GAD65-Seldeg with MST-HN, knobs-into-holes and arginine mutations	MASPGSGFWSFGSEDGSGDSENPGTARAWCQVAQKFTGGIG NKLCALLYGDAEKPAESGGSQPPRAAARKAACACDQKPCSC SKVDVNYAFLHATDLLPACDGERPTLAFLQDVMNILLQYVV KSFDRSTKVIDFHYPNELLQEYNWELADQPQNLEEILMHCQT TLKYAIKTGHPRYFNQLSTGLDMVGLAADWLTSTANTNMFT YEIAPVFVLLEYVTLKKMREIIGWPGGSGDGIFSPGGAISNMY AMMIARFKMFPEVKEKGMAALPRLIAFTSEHSHFSLKKGAAA LGIGTDSVILIKCDERGKMIPSDLERRILEAKQKGFVPFLVSAT AGTTVYGAFDPLLAVADICKKYKIWMHVDAAWGGGLLMSR KHKWKLSGVERANSVTWNPHKMMGVPLQCSALLVREEGLM QNCNQMHASYLFQQDKHYDLSYDTGDKALQCGRHVDVFKL WLMWRAKGTTGFEAHVDKCLELAEYLYNIIKNREGYEMVFD GKPQHTNVCFWYIPPSLRTLEDNEERMSRLSKVAPVIKARMM EYGTTMVSYQPLGDKVNFFRMVISNPAATHQDIDFLIEEIERL GQDLGGGGSVEPKSSDKTHTCPPCPAPELLRGPSVFLFPPKPK DTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKARPA PIEKTISKAKGQPREPQVTTLPPSRDELTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTFPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALKFHYTQKSLSLSPGK	32
AQP4-Seldeg with MST-HN, knobs-into-holes and arginine mutations	MSDRPTARRWGKCGPLCTRENIMVAFKGVWTQAFWKAVTA EFLAMLIFVLLSLGSTINWGGTEKPLPVDMVLISLCFGLSIATM VQCFGHISGGHINPAVTVAMVCTRKISIAKSVFYIAAQCLGAII GAGILYLVTPPSVVGGLGVTMVHGNLTAGHGLLVELIITFQLV FTIFASCDSKRTDVTGSIALAIGFSVAIGHLFAINYTGASMNPA RSFGPAVIMGNWENHWIYWVGPIIGAVLAGGLYEYVFCPDVE FKRRFKEAFSKAAQQTKGSYMEVEDNRSQVETDDLILKPGVV HVIDVDRGEEKKGKDQSGEVLSSVGGGGSVEPKSSDKTHTCP PCPAPELLRGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKARPAPIEKTISKAKGQPREPQVTTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTFPP VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALKFHYT QKSLSLSPGK	34

The DNA sequence of SEQ ID NO: 1 is of a polynucleotide encoding an exemplary MOG-Seldeg fusion protein (SEQ ID NO: 2) having mutations to increase FcRn binding, knobs-into-holes mutations and arginine mutations. The exemplary DNA and amino acid sequences of the MOG respectively of SEQ ID NO: 1 and 2 are of mouse origin.

In particular, the amino acid sequence of the exemplary MOG-Seldeg of SEQ ID NO: 2 forms a fusion protein

having, in order from N- to C-terminus, residues **1-117** of mouse (m) MOG, a first linker at residues **118-122**, an immunoglobulin hinge (human IgG1-derived) at residues **123-138**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **139-248**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **249-355**. The exemplary MOG-Seldeg of SEQ ID NO: 2 has mutations that increase FcRn binding at residues **160**, **162**, **164**, **341** and **342**, arginine mutations at residues **144** and **236**, and 'knobs-into-holes' mutations at residues **257** and **302**. The cysteine residue (**128**) that usually pairs with an immunoglobulin light chain is mutated to serine. The amino acid residue numbers referred to in SEQ ID NO: 2 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 3 is of a polynucleotide encoding an exemplary HER2-Seldeg fusion protein (SEQ ID NO: 4) having mutations to increase FcRn binding, knobs-into-holes mutations and arginine mutations.

In particular, the amino acid sequence of the exemplary HER2-Seldeg of SEQ ID NO: 4 forms a fusion protein having, in order from N- to C-terminus, residues **1-630** of HER2, a first linker at residues **631-636**, an immunoglobulin hinge (human IgG1-derived) at residues **637-650**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **651-760**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **761-867**. The exemplary HER2-Seldeg of SEQ ID NO: 4 has mutations that increase FcRn binding at residues **672**, **674**, **676**, **853** and **854**, arginine mutations at residues **656** and **748**, and 'knobs-into-holes' mutations at residues **769** and **814**. The cysteine residue (**640**) that usually pairs with an immunoglobulin light chain is mutated to serine. The amino acid residue numbers referred to in SEQ ID NO: 4 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 5 is of a polynucleotide encoding an exemplary Fc fragment (SEQ ID NO: 6), having mutations to increase FcRn binding, knobs-into-holes mutations and arginine mutations. The fusion protein of SEQ ID NO: 6 is configured, for example, for heterodimer formation with the MOG-Seldeg (SEQ ID NO: 2) or HER2-Seldeg (SEQ ID NO: 4) fusion.

In particular, the amino acid sequence of the exemplary Fc fragment of SEQ ID NO: 6 has, in order from N- to C-terminus, an immunoglobulin hinge (human IgG1-derived) at residues **1-16**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **17-126**, an immunoglobulin C113 domain (human IgG1l-derived) at residues **127-233**. The exemplary Fc fragment of SEQ ID NO: 6 has mutations that increase FcRn binding at residues **38**, **40**, **42**, **219** and **220**, arginine mutations at residues **22** and **114**, and 'knobs-into-holes' mutations at residues **150** and **191**. The cysteine residue (**6**) that usually pairs with an immunoglobulin light chain is mutated to serine. The amino acid residue numbers referred to in SEQ ID NO: 6 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 7 is of a polynucleotide encoding an exemplary MOG-Seldeg-PS fusion having knobs-into-holes mutations and arginine mutations, and the corresponding amino acid sequence of the encoded fusion protein is SEQ ID NO: 8.

In particular, the amino acid sequence of the exemplary MOG-Seldeg-PS fusion of SEQ ID NO: 8 has, in order from N- to C-terminus, residues **1-117** of mMOG, a first linker at residues **118-122**, an immunoglobulin hinge (human IgG1-derived) at residues **123-138**, an immunoglobulin C12 domain (human IgG1-derived) at residues **139-248**, an immunoglobulin C13 domain (human IgG1-derived) at residues **249-355**. The exemplary MOG-Seldeg-PS of SEQ ID NO: 8 has arginine mutations at residues **144** and **236**, and 'knobs-into-holes' mutations at residues **257** and **302**. The cysteine residue (**128**) that pairs with an immunoglobulin light chain is mutated to serine Residues **141-266** of the C2A PS-binding domain of synaptotagmin (Syt1) (shown as residues **361486**) are fused to the C-terminus of the CH3 domain via a GGGGS (SEQ ID NO: 38) linker peptide (residues **356-360**). The amino acid residue numbers referred to in SEQ ID NO: 8 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 9 is of a polynucleotide encoding an exemplary Fc-Syt1 fusion (SEQ ID NO: 10) having knobs-into-holes mutations and arginine mutations, configured for heterodimer formation, for example, with the MOG-Seldeg-PS (SEQ ID NO: 8).

In particular, the amino acid sequence of the exemplary Fc-Syt1 fusion of SEQ ID NO: 10 has, in order from N- to C-terminus, an immunoglobulin hinge (human IgG1-derived) at residues **1-16**, an immunoglobulin C12 domain (human IgG1-derived) at residues **17-126**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **126-233**. The exemplary Fc-Syt1 fusion protein of SEQ ID NO: 10 has arginine mutations at residues **22** and **114** and 'knobs-into-holes' mutations at residues **150** and **191**. The cysteine residue (**6**) that usually pairs with an immunoglobulin light chain is mutated to serine Residues **141-266** of the C2A PS-binding domain of synaptotagmin (Syt1) (shown as residues **239-364**) are fused to the C-terminus of the CH3 domain via a GGGGS (SEQ ID NO: 38) linker peptide (residues **234-238**). The amino acid residue numbers referred to in SEQ ID NO: 10 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 11 is of a polynucleotide encoding an exemplary MOG-Seldeg-PS fusion (SEQ ID NO: 12) having knobs-into-holes mutations, electrostatic steering mutations and arginine mutations.

In particular, the amino acid sequence of the exemplary MOG-Seldeg-PS fusion of SEQ ID NO: 12 has, in order from N- to C-terminus, residues **1-117** of mMOG, a first linker at residues **118-122**, an immunoglobulin hinge (human IgG1-derived) at residues **123-138**, an immunoglobulin C112 domain (human IgG1-derived) at residues **139-248**, an immunoglobulin C13 domain (human IgG1-derived) at residues **249-355**. The exemplary MOG-Seldeg-PS of SEQ ID NO: 12 has arginine mutations at residues **144** and **236**, electrostatic steering mutations at residues **300** and **317** and 'knobs-into-holes' mutations at residues **257** and **302**. The cysteine residue (**128**) that pairs with an immunoglobulin light chain is mutated to serine Residues **141-266** of the C2A PS-binding domain of synaptotagmin (Syt1) (shown as residues **361-486**) are fused to the C-terminus of the C13 domain via a GGGS linker peptide (residues **356-360**). The amino acid residue numbers referred to in SEQ ID NO: 12 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 13 is of a polynucleotide encoding an exemplary Fc-Syt1 fusion (SEQ ID NO: 14) having knobs-into-holes mutations, electrostatic steering mutations and arginine mutations, configured, for example, for heterodimer formation with the MOG-Seldeg-PS (SEQ ID NO: 12).

In particular, the amino acid sequence of the exemplary Fc-Syt1 fusion protein of SEQ ID NO: 14 has, in order from N- to C-terminus, an immunoglobulin hinge (human IgG1-derived) at residues **1-16**, an immunoglobulin CH2 domain

(human IgG1-derived) at residues **17-126**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **127-233**. The exemplary MOG-Seldeg-PS of SEQ ID NO: 14 has arginine mutations at residues **22** and **114**, electrostatic steering mutations at residues **143** and **185** and 'knobs-into-holes' mutations at residues **150** and **191**. The cysteine residue (**6**) that pairs with an immunoglobulin light chain is mutated to serine. Residues **141-266** of the C2A PS-binding domain of synaptotagmin (Syt1) (shown as residues **239-364**) are fused to the C-terminus of the CH3 domain via a GGGGS (SEQ ID NO: 38) linker peptide (residues **234-238**) The amino acid residue numbers referred to in SEQ ID NO: 14 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 15 is of a polynucleotide encoding an exemplary MOG-Seldeg-TfR fusion protein (SEQ ID NO: 16) comprising a TfR-specific antibody heavy chain with knobs into holes mutations.

In particular, the amino acid sequence of the exemplary TfR-specific antibody heavy chain-MOG fusion (MOG-Seldeg-TfR) of SEQ ID NO: 16 has, in order from N- to C-terminus, a TfR-specific VH domain at residues **1-116**, an immunoglobulin CH1 domain (human IgG1-derived) at residues **117-213**, an immunoglobulin hinge (human IgG1-derived) at residues **214-229**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **230-339**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **340-446**. The exemplary TfR-specific antibody heavy chain of SEQ ID NO: 16 has 'knobs-into-holes' mutations at residues **348** and **393**. Residues **1-117** of mMOG (shown as residues **452-568**) are fused to the C-terminus of the C13 domain via a GGGGS (SEQ ID NO: 38) linker peptide (residues **447-451**). The amino acid residue numbers referred to in SEQ ID NO: 16 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 17 is of a polynucleotide encoding an exemplary TfR-specific antibody heavy chain. The encoded fusion protein (SEQ ID NO: 18) having knobs into holes mutations is configured, for example, for heterodimer formation with the MOG-Seldeg-TfR fusion (SEQ ID NO: 16).

In particular, the amino acid sequence of the exemplary TfR-specific antibody heavy chain of SEQ ID NO: 18 for heterodimer formation with the TfR-specific heavy chain-MOG fusion (SEQ ID NO: 16) has, in order from N- to C-terminus, of a TfR-specific VH domain at residues **1-116**, an immunoglobulin CH1 domain (human IgG1-derived) at residues **117-213**, an immunoglobulin hinge (human IgG1-derived) at residues **214-229** an immunoglobulin CH2 domain (human IgG1-derived) at residues **230-339**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **340-446**. The exemplary TfR-specific antibody heavy chain of SEQ ID NO: 18 has 'knobs-into-holes' mutations at residues **363** and **404**. The amino acid residue numbers referred to in SEQ ID NO: 18 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 19 is of a polynucleotide encoding an exemplary light chain of a TfR-specific antibody (SEQ ID NO: 20) and is configured, for example, for heterodimer formation with the MOG-Seldeg-TfR fusion (SEQ ID NO: 16) and TfR-specific antibody heavy chain (SEQ ID NO: 18).

In particular, the amino acid sequence of the exemplary TfR-specific antibody light chain of SEQ ID NO: 20 has, in order from N- to C-terminus a TfR-specific VL domain at residues **1-107**, and an immunoglobulin CL domain (human Cκ) at residues **108-213**. The amino acid residue numbers referred to in SEQ ID NO: 20 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 21 is of a polynucleotide encoding an exemplary MOG-Seldeg-TfR fusion protein (SEQ ID NO: 22) having a TfR-specific antibody heavy chain with arginine mutations, and knobs-into-holes mutations.

In particular, the amino acid sequence of the exemplary TfR-specific antibody heavy chain-MOG fusion (MOG-Seldeg-TfR) of SEQ ID NO: 22 has, in order from N- to C-terminus, a TfR-specific VH domain at residues **1-116**, an immunoglobulin CH1 domain (human IgG1-derived) at residues **117-213**, an immunoglobulin hinge (human IgG1-derived) at residues **214-229**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **230-339**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **340-446**. The exemplary TfR-specific antibody heavy chain of SEQ ID NO: 22 has arginine mutations at residues **235** and **327**, and 'knobs-into-holes' mutations at residues **348** and **393**. Residues **1-117** of mMOG (shown as residues **452-568**) are fused to the C-terminus of the C311 domain via a GGGGS (SEQ ID NO: 38) linker peptide (residues **447-451**). The amino acid residue numbers referred to in SEQ ID NO: 22 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 23 is of a polynucleotide encoding an exemplary TfR-specific antibody heavy chain (SEQ ID NO: 24) having arginine mutations, and knobs-into-holes mutations, and is configured, for example, for heterodimer formation with the MOG-Seldeg-TfR fusion (SEQ ID NO: 22).

In particular, the amino acid sequence of the exemplary TfR-specific antibody heavy chain of SEQ ID NO: 24 has, in order from N- to C-terminus, a TfR-specific VH domain at residues **1-116**, an immunoglobulin CH1 domain (human IgG1-derived) at residues **117-213**, an immunoglobulin hinge (human IgG1-derived) at residues **214-229** an immunoglobulin CH2 domain (human IgG1-derived) at residues **230-339**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **340-446**. The TfR-specific antibody heavy chain of SEQ ID NO: 24 has arginine mutations at residues **235** and **327**, and 'knobs-into-holes' mutations at residues **363** and **404**). The amino acid residue numbers referred to in SEQ ID NO: 24 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ TD NO: 25 is of a polynucleotide encoding an exemplary HER2-Seldeg fusion protein (SEQ ID NO: 26) having mutations to increase FcRn binding, and knobs-into-holes mutations.

In particular, the amino acid sequence of the exemplary variant HER2-Seldeg of SEQ ID NO: 26 forms a fusion protein having, in order from N- to C-terminus, residues **1-630** of HER2, a first linker at residues **631-636**, an immunoglobulin hinge (human IgG1-derived) at residues **637-650**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **651-760**, an immunoglobulin C13 domain (human IgG1-derived) at residues **761-867**. The HER2-Seldeg of SEQ ID NO: 26 has mutations that increase FcRn binding at residues **672**, **674**, **676**, **853** and **854**, and 'knobs-into-holes' mutations at residues **769** and **814**. The cysteine residue (**640**) that usually pairs with an immunoglobulin light chain is mutated to serine. The amino acid residue numbers referred to in SEQ ID NO: 26 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 27 is of a polynucleotide encoding an exemplary Fc fragment (SEQ ID NO: 28) having mutations to increase FcRn binding, and knobs-into-holes mutations, and is configured, for example, for heterodimer formation with the HER2-Seldeg (SEQ ID NO: 26).

In particular, the amino acid sequence of the exemplary variant Fc fragment of SEQ ID NO: 28 has, in order from N- to C-terminus, an immunoglobulin hinge (human IgG1-derived) at residues **1-16**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **17-126**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **127-233**. The variant Fc fragment of SEQ ID NO: 28 has mutations that increase FcRn binding at residues **38**, **40**, **42**, **219** and **220**, and 'knobs-into-holes' mutations at residues **150** and **191**. The cysteine residue (**6**) that usually pairs with an immunoglobulin light chain is mutated to serine. The amino acid residue numbers referred to in SEQ ID NO: 28 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 29 is of a polynucleotide encoding an exemplary prostate-specific membrane antigen (PSMA)-Seldeg fusion protein (SEQ ID NO: 30) having mutations to increase FcRn binding, knobs-into-holes mutations and arginine mutations. This fusion protein will form heterodimers, for example, with an exemplary Fc fragment (SEQ ID NO: 6).

In particular, the amino acid sequence of the exemplary variant PSMA-Seldeg of SEQ ID NO: 30 forms a fusion protein having, in order from N- to C-terminus, an immunoglobulin hinge (human IgG1-derived) at residues **1-16**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **17-126**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **127-233** fused at the C-terminus via a linker at residues **234-238** to the extracellular domain (residues **239-945**) of PSMA The variant PSMA-Seldeg of SEQ ID NO: 30 has mutations that increase FcRn binding at residues **38**, **40**, **42**, **219** and **220**, arginine mutations at residues **22** and **114**, and 'knobs-into-holes' mutations at residues **135** and **180**. The cysteine residue (**6**) that usually pairs with an immunoglobulin light chain is mutated to serine. The amino acid residue numbers referred to in SEQ ID NO: 30 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 31 is of a polynucleotide encoding an exemplary GAD65-Seldeg fusion protein (SEQ ID NO: 32) having mutations to increase FcRn binding, knobs-into-holes mutations and arginine mutations. This fusion protein will form heterodimers, for example, with an exemplary Fc fragment (SEQ ID NO: 6).

In particular, the amino acid sequence of the exemplary variant GAD65-Seldeg of SEQ ID NO: 32 forms a fusion protein having, in order from N- to C-terminus, residues **1-585** of human glutamic acid carboxylase 65 (GAD6S), a first linker at residues **586-590**, an immunoglobulin hinge (human IgG1-derived) at residues **591-606**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **607-716**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **717-823**. The variant GAD65-Seldeg of SEQ ID NO: 32 has mutations that increase FcRn binding at residues **628**, **630**, **632**, **809** and **810**, arginine mutations at residues **612** and **704**, and 'knobs-into-holes' mutations at residues **725** and **770**. The cysteine residue (**596**) that usually pairs with an immunoglobulin light chain is mutated to serine. The amino acid residue numbers referred to in SEQ ID NO: 32 are those of the protein sequence, and do not refer to the EU numbering convention.

The DNA sequence of SEQ ID NO: 33 is of a polynucleotide encoding an exemplary aquaporin 4-Seldeg fusion protein (SEQ ID NO: 34) having mutations to increase FcRn binding, knobs-into-holes mutations and arginine mutations. This fusion protein will form heterodimers, for example, with an exemplary Fc fragment (SEQ ID NO: 6).

In particular, the amino acid sequence of the exemplary variant aquaporin 4 (AQP4)-Seldeg of SEQ ID NO: 34 forms a fusion protein having, in order from N- to C-terminus, residues **1-323** of human aquaporin 4, a first linker at residues **324-328**, an immunoglobulin hinge (human IgG1-derived) at residues **329-344**, an immunoglobulin CH2 domain (human IgG1-derived) at residues **345-454**, an immunoglobulin CH3 domain (human IgG1-derived) at residues **455-561**. The variant AQP4-Seldeg of SEQ ID NO: 34 has mutations that increase FcRn binding at residues **366**, **368**, **370**, **547**,**548**, arginine mutations at residues **350** and **442**, and 'knobs-into-holes' mutations at residues **463** and **508**. The cysteine residue (**334**) that usually pairs with an immunoglobulin light chain is mutated to serine. The amino acid residue numbers referred to in SEQ ID NO: 34 are those of the protein sequence, and do not refer to the EU numbering convention.

The above disclosed subject matter is to be considered illustrative, and not restrictive, and the appended claims are intended to cover all such modifications, enhancements, and other embodiments which fall within the true spirit and scope of the present disclosure. Thus, to the maximum extent allowed by law, the scope of the present disclosure is to be determined by the broadest permissible interpretation of the following claims and their equivalents, and shall not be restricted or limited by the foregoing detailed description.

As used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. The term "plurality" includes two or more referents unless the content clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains.

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ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac   2160

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag   2220

tgcaaggtct ccaacaaagc ccgcccagcc cccatcgaga aaaccatctc caaagccaaa   2280

gggcagcccc gagaaccaca ggtgaccacc ctgccccat cccgggatga gctgaccaag   2340

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   2400

tgggagagca atgggcagcc ggagaacaac tacaagacct tccctcccgt gctggactcc   2460

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   2520

aacgtcttct catgctctgt gatgcatgag gctctgaaat tccactacac gcagaagagc   2580

ctctccctgt ctcctggtaa a                                             2601
```

<210> SEQ ID NO 4
<211> LENGTH: 867
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

```
Thr Gln Val Cys Thr Gly Thr Asp Met Lys Leu Arg Leu Pro Ala Ser
1               5                  10                  15

Pro Glu Thr His Leu Asp Met Leu Arg His Leu Tyr Gln Gly Cys Gln
            20                  25                  30

Val Val Gln Gly Asn Leu Glu Leu Thr Tyr Leu Pro Thr Asn Ala Ser
        35                  40                  45

Leu Ser Phe Leu Gln Asp Ile Gln Glu Val Gln Gly Tyr Val Leu Ile
    50                  55                  60

Ala His Asn Gln Val Arg Gln Val Pro Leu Gln Arg Leu Arg Ile Val
65                  70                  75                  80

Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr Ala Leu Ala Val Leu Asp
                85                  90                  95

Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro Val Thr Gly Ala Ser Pro
            100                 105                 110
```

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```
Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser Leu Thr Glu Ile Leu Lys
        115                 120                 125

Gly Gly Val Leu Ile Gln Arg Asn Pro Gln Leu Cys Tyr Gln Asp Thr
    130                 135                 140

Ile Leu Trp Lys Asp Ile Phe His Lys Asn Asn Gln Leu Ala Leu Thr
145                 150                 155                 160

Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys His Pro Cys Ser Pro Met
                165                 170                 175

Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser Ser Glu Asp Cys Gln Ser
            180                 185                 190

Leu Thr Arg Thr Val Cys Ala Gly Gly Cys Ala Arg Cys Lys Gly Pro
        195                 200                 205

Leu Pro Thr Asp Cys Cys His Glu Gln Cys Ala Ala Gly Cys Thr Gly
    210                 215                 220

Pro Lys His Ser Asp Cys Leu Ala Cys Leu His Phe Asn His Ser Gly
225                 230                 235                 240

Ile Cys Glu Leu His Cys Pro Ala Leu Val Thr Tyr Asn Thr Asp Thr
                245                 250                 255

Phe Glu Ser Met Pro Asn Pro Glu Gly Arg Tyr Thr Phe Gly Ala Ser
            260                 265                 270

Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu Ser Thr Asp Val Gly Ser
        275                 280                 285

Cys Thr Leu Val Cys Pro Leu His Asn Gln Glu Val Thr Ala Glu Asp
    290                 295                 300

Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys Pro Cys Ala Arg Val Cys
305                 310                 315                 320

Tyr Gly Leu Gly Met Glu His Leu Arg Glu Val Arg Ala Val Thr Ser
                325                 330                 335

Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys Lys Ile Phe Gly Ser Leu
            340                 345                 350

Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp Pro Ala Ser Asn Thr Ala
        355                 360                 365

Pro Leu Gln Pro Glu Gln Leu Gln Val Phe Glu Thr Leu Glu Glu Ile
    370                 375                 380

Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro Asp Ser Leu Pro Asp Leu
385                 390                 395                 400

Ser Val Phe Gln Asn Leu Gln Val Ile Arg Gly Arg Ile Leu His Asn
                405                 410                 415

Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu Gly Ile Ser Trp Leu Gly
            420                 425                 430

Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly Leu Ala Leu Ile His His
        435                 440                 445

Asn Thr His Leu Cys Phe Val His Thr Val Pro Trp Asp Gln Leu Phe
    450                 455                 460

Arg Asn Pro His Gln Ala Leu Leu His Thr Ala Asn Arg Pro Glu Asp
465                 470                 475                 480

Glu Cys Val Gly Glu Gly Leu Ala Cys His Gln Leu Cys Ala Arg Gly
                485                 490                 495

His Cys Trp Gly Pro Gly Pro Thr Gln Cys Val Asn Cys Ser Gln Phe
            500                 505                 510

Leu Arg Gly Gln Glu Cys Val Glu Glu Cys Arg Val Leu Gln Gly Leu
        515                 520                 525

Pro Arg Glu Tyr Val Asn Ala Arg His Cys Leu Pro Cys His Pro Glu
```

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```
    530                 535                 540

Cys Gln Pro Gln Asn Gly Ser Val Thr Cys Phe Gly Pro Glu Ala Asp
545                 550                 555                 560

Gln Cys Val Ala Cys Ala His Tyr Lys Asp Pro Pro Phe Cys Val Ala
                565                 570                 575

Arg Cys Pro Ser Gly Val Lys Pro Asp Leu Ser Tyr Met Pro Ile Trp
            580                 585                 590

Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln Pro Cys Pro Ile Asn Cys
        595                 600                 605

Thr His Ser Cys Val Asp Leu Asp Asp Lys Gly Cys Pro Ala Glu Gln
    610                 615                 620

Arg Ala Ser Pro Leu Thr Ile Glu Gly Arg Met Asp Pro Lys Ser Ser
625                 630                 635                 640

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Arg
                645                 650                 655

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr
            660                 665                 670

Ile Thr Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        675                 680                 685

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    690                 695                 700

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
705                 710                 715                 720

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                725                 730                 735

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Arg Pro Ala Pro Ile
            740                 745                 750

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        755                 760                 765

Thr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    770                 775                 780

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
785                 790                 795                 800

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Phe Pro Pro
                805                 810                 815

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            820                 825                 830

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        835                 840                 845

His Glu Ala Leu Lys Phe His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    850                 855                 860

Pro Gly Lys
865
```

<210> SEQ ID NO 5
<211> LENGTH: 699
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

```
gttgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaactc     60

ctgaggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct ctacatcact    120

cgggaacctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag    180
```

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```
ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag    240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg    300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc gcccagcccc catcgagaaa    360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc    420

cgggatgagc tgaccaagaa ccaggtccac ctgacctgcc tggtcaaagg cttctatccc    480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg    540

cctcccgtgc tggactccga cggctccttc gccctctaca gcaagctcac cgtggacaag    600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgaaattc    660

cactacacgc agaagagcct ctccctgtct ccgggtaaa                           699


<210> SEQ ID NO 6
<211> LENGTH: 233
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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

Ala Pro Glu Leu Leu Arg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys Val
        35                  40                  45

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

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

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

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    130                 135                 140

Thr Lys Asn Gln Val His Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Ala Leu
            180                 185                 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu Lys Phe His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225                 230


<210> SEQ ID NO 7
<211> LENGTH: 1458
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7
```

-continued

```
ggacaattca gagtgatagg accagggtat cccatccggg ctttagttgg ggatgaagca     60

gagctgccgt gccgcatctc tcctgggaaa aatgccacgg gcatggaggt gggttggtac    120

cgttctccct tctcaagagt ggttcacctc taccgaaatg gcaaggacca agatgcagag    180

caagcacctg aataccgggg acgcacagag cttctgaaag agactatcag tgagggaaag    240

gttaccctta ggattcagaa cgtgagattc tcagatgaag gaggctacac ctgcttcttc    300

agagaccact cttaccaaga agaggcagca atggagttga aagtggaaga tggaggcggt    360

ggatcagttg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct    420

gaactcctga ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg    480

atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag    540

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg    600

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac    660

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagcccgccc agcccccatc    720

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgac caccctgccc    780

ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc    840

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacaag    900

accttccctc ccgtgctgga ctccgacggc tccttcttcc tctacagcaa gctcaccgtg    960

gacaagagca ggtggcagca ggggaacgtc ttctcatgct ctgtgatgca tgaggctctg   1020

cataaccact acacgcagaa gagcctctcc ctgtctccgg gtaaaggagg cggtggatca   1080

gagaaactgg gaaaacttca gtattcactg gattatgatt tccaaaataa ccagctgctg   1140

gtagggatca ttcaggctgc cgaactgccc gccttggaca tgggggcac atctgatcct   1200

tacgtgaaag tgtttctgct acctgataag aagaagaaat ttgagacaaa agtccaccga   1260

aaaaccctta atcctgtctt caatgagcaa tttactttca aggtaccata ctcggaattg   1320

ggtggcaaaa ccctagtgat ggctgtatat gattttgatc gtttctctaa gcatgacatc   1380

attggagaat ttaaagtccc tatgaacaca gtggattttg gccatgtaac tgaggaatgg   1440

cgtgacctgc aaagtgct                                                 1458
```

<210> SEQ ID NO 8
<211> LENGTH: 486
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

```
Gly Gln Phe Arg Val Ile Gly Pro Gly Tyr Pro Ile Arg Ala Leu Val
1               5                  10                  15

Gly Asp Glu Ala Glu Leu Pro Cys Arg Ile Ser Pro Gly Lys Asn Ala
            20                  25                  30

Thr Gly Met Glu Val Gly Trp Tyr Arg Ser Pro Phe Ser Arg Val Val
        35                  40                  45

His Leu Tyr Arg Asn Gly Lys Asp Gln Asp Ala Glu Gln Ala Pro Glu
    50                  55                  60

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

Val Thr Leu Arg Ile Gln Asn Val Arg Phe Ser Asp Glu Gly Gly Tyr
                85                  90                  95

Thr Cys Phe Phe Arg Asp His Ser Tyr Gln Glu Glu Ala Ala Met Glu
            100                 105                 110
```

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```
Leu Lys Val Glu Asp Gly Gly Gly Gly Ser Val Glu Pro Lys Ser Ser
        115                 120                 125

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Arg
    130                 135                 140

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
145                 150                 155                 160

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
                165                 170                 175

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
            180                 185                 190

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
        195                 200                 205

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
    210                 215                 220

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Arg Pro Ala Pro Ile
225                 230                 235                 240

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
                245                 250                 255

Thr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
            260                 265                 270

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
        275                 280                 285

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Phe Pro Pro
    290                 295                 300

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
305                 310                 315                 320

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
                325                 330                 335

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            340                 345                 350

Pro Gly Lys Gly Gly Gly Gly Ser Glu Lys Leu Gly Lys Leu Gln Tyr
        355                 360                 365

Ser Leu Asp Tyr Asp Phe Gln Asn Asn Gln Leu Leu Val Gly Ile Ile
    370                 375                 380

Gln Ala Ala Glu Leu Pro Ala Leu Asp Met Gly Gly Thr Ser Asp Pro
385                 390                 395                 400

Tyr Val Lys Val Phe Leu Leu Pro Asp Lys Lys Lys Lys Phe Glu Thr
                405                 410                 415

Lys Val His Arg Lys Thr Leu Asn Pro Val Phe Asn Glu Gln Phe Thr
            420                 425                 430

Phe Lys Val Pro Tyr Ser Glu Leu Gly Gly Lys Thr Leu Val Met Ala
        435                 440                 445

Val Tyr Asp Phe Asp Arg Phe Ser Lys His Asp Ile Ile Gly Glu Phe
    450                 455                 460

Lys Val Pro Met Asn Thr Val Asp Phe Gly His Val Thr Glu Glu Trp
465                 470                 475                 480

Arg Asp Leu Gln Ser Ala
                485
```

<210> SEQ ID NO 9
<211> LENGTH: 1092
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

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```
gttgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaactc     60

ctgaggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc    120

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag    180

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag    240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg    300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc gcccagcccc catcgagaaa    360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc    420

cgggatgagc tgaccaagaa ccaggtccac ctgacctgcc tggtcaaagg cttctatccc    480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg    540

cctcccgtgc tggactccga cggctccttc gccctctaca gcaagctcac cgtggacaag    600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac    660

cactacacgc agaagagcct ctccctgtct ccgggtaaag gaggcggtgg atcagagaaa    720

ctgggaaaac ttcagtattc actggattat gatttccaaa ataaccagct gctggtaggg    780

atcattcagg ctgccgaact gcccgccttg gacatggggg gcacatctga tccttacgtg    840

aaagtgtttc tgctacctga taagaagaag aaatttgaga caaaagtcca ccgaaaaacc    900

cttaatcctg tcttcaatga gcaatttact ttcaaggtac catactcgga attgggtggc    960

aaaaccctag tgatggctgt atatgatttt gatcgtttct ctaagcatga catcattgga   1020

gaatttaaag tccctatgaa cacagtggat tttggccatg taactgagga atggcgtgac   1080

ctgcaaagtg ct                                                       1092
```

```
<210> SEQ ID NO 10
<211> LENGTH: 364
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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

Ala Pro Glu Leu Leu Arg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        35                  40                  45

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

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

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

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    130                 135                 140

Thr Lys Asn Gln Val His Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175
```

```
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Ala Leu
            180                 185                 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Glu Lys
225                 230                 235                 240

Leu Gly Lys Leu Gln Tyr Ser Leu Asp Tyr Asp Phe Gln Asn Asn Gln
                245                 250                 255

Leu Leu Val Gly Ile Ile Gln Ala Ala Glu Leu Pro Ala Leu Asp Met
            260                 265                 270

Gly Gly Thr Ser Asp Pro Tyr Val Lys Val Phe Leu Leu Pro Asp Lys
        275                 280                 285

Lys Lys Lys Phe Glu Thr Lys Val His Arg Lys Thr Leu Asn Pro Val
    290                 295                 300

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

Lys Thr Leu Val Met Ala Val Tyr Asp Phe Asp Arg Phe Ser Lys His
                325                 330                 335

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

His Val Thr Glu Glu Trp Arg Asp Leu Gln Ser Ala
        355                 360


<210> SEQ ID NO 11
<211> LENGTH: 1458
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

ggacaattca gagtgatagg accagggtat cccatccggg ctttagttgg ggatgaagca     60

gagctgccgt gccgcatctc tcctgggaaa aatgccacgg gcatggaggt gggttggtac    120

cgttctccct tctcaagagt ggttcacctc taccgaaatg gcaaggacca agatgcagag    180

caagcacctg aataccgggg acgcacagag cttctgaaag agactatcag tgagggaaag    240

gttaccctta ggattcagaa cgtgagattc tcagatgaag gaggctacac ctgcttcttc    300

agagaccact cttaccaaga agaggcagca atggagttga aagtggaaga tggaggcggt    360

ggatcagttg agcccaaatc ttctgacaaa actcacacat gcccaccgtg cccagcacct    420

gaactcctga ggggaccgtc agtcttcctc ttcccccaa aacccaagga caccctcatg    480

atctcccgga cccctgaggt cacatgcgtg gtggtggacg tgagccacga agaccctgag    540

gtcaagttca actggtacgt ggacggcgtg gaggtgcata atgccaagac aaagccgcgg    600

gaggagcagt acaacagcac gtaccgtgtg gtcagcgtcc tcaccgtcct gcaccaggac    660

tggctgaatg gcaaggagta caagtgcaag gtctccaaca aagcccgccc agcccccatc    720

gagaaaacca tctccaaagc caaagggcag ccccgagaac cacaggtgac caccctgccc    780

ccatcccggg atgagctgac caagaaccag gtcagcctga cctgcctggt caaaggcttc    840

tatcccagcg acatcgccgt ggagtgggag agcaatgggc agccggagaa caactacgac    900

accttccctc ccgtgctgga ctccgacggc tccttcttcc tctacagcga cctcaccgtg    960

gacaagagca ggtggcagca ggggaacgtc ttctcatgct ctgtgatgca tgaggctctg   1020
```

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cataaccact acacgcagaa gagcctctcc ctgtctccgg gtaaaggagg cggtggatca 1080

gagaaactgg gaaaacttca gtattcactg gattatgatt tccaaaataa ccagctgctg 1140

gtagggatca ttcaggctgc cgaactgccc gccttggaca tgggggggcac atctgatcct 1200

tacgtgaaag tgtttctgct acctgataag aagaagaaat ttgagacaaa agtccaccga 1260

aaaaccctta atcctgtctt caatgagcaa tttactttca aggtaccata ctcggaattg 1320

ggtggcaaaa ccctagtgat ggctgtatat gattttgatc gtttctctaa gcatgacatc 1380

attggagaat ttaaagtccc tatgaacaca gtggattttg gccatgtaac tgaggaatgg 1440

cgtgacctgc aaagtgct 1458

<210> SEQ ID NO 12
<211> LENGTH: 486
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Gly Gln Phe Arg Val Ile Gly Pro Gly Tyr Pro Ile Arg Ala Leu Val
1 5 10 15

Gly Asp Glu Ala Glu Leu Pro Cys Arg Ile Ser Pro Gly Lys Asn Ala
20 25 30

Thr Gly Met Glu Val Gly Trp Tyr Arg Ser Pro Phe Ser Arg Val Val
35 40 45

His Leu Tyr Arg Asn Gly Lys Asp Gln Asp Ala Glu Gln Ala Pro Glu
50 55 60

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

Val Thr Leu Arg Ile Gln Asn Val Arg Phe Ser Asp Glu Gly Gly Tyr
85 90 95

Thr Cys Phe Phe Arg Asp His Ser Tyr Gln Glu Glu Ala Ala Met Glu
100 105 110

Leu Lys Val Glu Asp Gly Gly Gly Gly Ser Val Glu Pro Lys Ser Ser
115 120 125

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Arg
130 135 140

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
145 150 155 160

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
165 170 175

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
180 185 190

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
195 200 205

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
210 215 220

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Arg Pro Ala Pro Ile
225 230 235 240

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
245 250 255

Thr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
260 265 270

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
275 280 285

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Asp Thr Phe Pro Pro

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```
    290                 295                 300

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Asp Leu Thr Val
305                 310                 315                 320

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
                325                 330                 335

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
            340                 345                 350

Pro Gly Lys Gly Gly Gly Gly Ser Glu Lys Leu Gly Lys Leu Gln Tyr
        355                 360                 365

Ser Leu Asp Tyr Asp Phe Gln Asn Asn Gln Leu Leu Val Gly Ile Ile
    370                 375                 380

Gln Ala Ala Glu Leu Pro Ala Leu Asp Met Gly Gly Thr Ser Asp Pro
385                 390                 395                 400

Tyr Val Lys Val Phe Leu Leu Pro Asp Lys Lys Lys Lys Phe Glu Thr
                405                 410                 415

Lys Val His Arg Lys Thr Leu Asn Pro Val Phe Asn Glu Gln Phe Thr
            420                 425                 430

Phe Lys Val Pro Tyr Ser Glu Leu Gly Gly Lys Thr Leu Val Met Ala
        435                 440                 445

Val Tyr Asp Phe Asp Arg Phe Ser Lys His Asp Ile Ile Gly Glu Phe
    450                 455                 460

Lys Val Pro Met Asn Thr Val Asp Phe Gly His Val Thr Glu Glu Trp
465                 470                 475                 480

Arg Asp Leu Gln Ser Ala
                485


<210> SEQ ID NO 13
<211> LENGTH: 1092
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

gttgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaactc     60

ctgaggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc    120

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag    180

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag    240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg    300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc gcccagcccc catcgagaaa    360

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc    420

cgggataagc tgaccaagaa ccaggtccac ctgacctgcc tggtcaaagg cttctatccc    480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg    540

cctcccgtgc tgaagtccga cggctccttc gccctctaca gcaagctcac cgtggacaag    600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac    660

cactacacgc agaagagcct ctccctgtct ccgggtaaag gaggcggtgg atcagagaaa    720

ctgggaaaac ttcagtattc actggattat gatttccaaa ataaccagct gctggtaggg    780

atcattcagg ctgccgaact gcccgccttg gacatggggg gcacatctga tccttacgtg    840

aaagtgtttc tgctacctga taagaagaag aaatttgaga caaaagtcca ccgaaaaacc    900

cttaatcctg tcttcaatga gcaatttact ttcaaggtac catactcgga attgggtggc    960

aaaaccctag tgatggctgt atatgatttt gatcgtttct ctaagcatga catcattgga   1020
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gaatttaaag tccctatgaa cacagtggat tttggccatg taactgagga atggcgtgac 1080

ctgcaaagtg ct 1092

<210> SEQ ID NO 14
<211> LENGTH: 364
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

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

Ala Pro Glu Leu Leu Arg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
35 40 45

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

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

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

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

Thr Lys Asn Gln Val His Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Lys Ser Asp Gly Ser Phe Ala Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Glu Lys
225 230 235 240

Leu Gly Lys Leu Gln Tyr Ser Leu Asp Tyr Asp Phe Gln Asn Asn Gln
245 250 255

Leu Leu Val Gly Ile Ile Gln Ala Ala Glu Leu Pro Ala Leu Asp Met
260 265 270

Gly Gly Thr Ser Asp Pro Tyr Val Lys Val Phe Leu Leu Pro Asp Lys
275 280 285

Lys Lys Lys Phe Glu Thr Lys Val His Arg Lys Thr Leu Asn Pro Val
290 295 300

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

Lys Thr Leu Val Met Ala Val Tyr Asp Phe Asp Arg Phe Ser Lys His
325 330 335

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

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His Val Thr Glu Glu Trp Arg Asp Leu Gln Ser Ala
355 360

<210> SEQ ID NO 15
<211> LENGTH: 1704
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

gaggtgcagc tggtgcagtc cggcgccgag gtgaagaagc ccggcgcctc cgtgaaggtg 60

tcctgcaagg cctccggcta caccttcacc tcctactgga tgcactgggt gcggcaggcc 120

cccggccagc ggctggagtg gatcggcgag atcaacccca ccaacggccg gaccaactac 180

atcgagaagt tcaagtcccg ggccaccctg accgtggaca agtccgcctc caccgcctac 240

atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgc ccggggcacc 300

cgggcctacc actactgggg ccagggcacc atggtgaccg tgtcctccgc ctccaccaag 360

ggcccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc 420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc 540

ctcagcagcg tggtgactgt gccctccagc agcttgggca cccagaccta catctgcaac 600

gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttgagcccaa atcttgtgac 660

aaaactcaca catgcccacc gtgcccagca cctgaactcc tgggggggacc gtcagtcttc 720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacatgc 780

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt 900

gtggtcagcg tccttaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc 960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg 1020

cagccccgag aaccacaggt gaccaccctg cccccatccc gggatgagct gaccaagaac 1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg 1140

gagagcaatg ggcagccgga gaacaactac aagaccttcc ctcccgtgct ggactccgac 1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac 1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc 1320

tccctgtctc cgggtaaagg aggcggtgga tcaggacaat tcagagtgat aggaccaggg 1380

tatcccatcc gggctttagt tggggatgaa gcagagctgc cgtgccgcat ctctcctggg 1440

aaaaatgcca cgggcatgga ggtgggttgg taccgttctc ccttctcaag agtggttcac 1500

ctctaccgaa atggcaagga ccaagatgca gagcaagcac ctgaataccg gggacgcaca 1560

gagcttctga aagagactat cagtgaggga aaggttaccc ttaggattca gaacgtgaga 1620

ttctcagatg aaggaggcta cacctgcttc ttcagagacc actcttacca agaagaggca 1680

gcaatggagt tgaaagtgga agat 1704

<210> SEQ ID NO 16
<211> LENGTH: 568
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

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

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

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

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
    50                  55                  60

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

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

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

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

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

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

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

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

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

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

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

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

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

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

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

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

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

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

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

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

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

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430
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Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly
       435                 440                 445

Gly Gly Ser Gly Gln Phe Arg Val Ile Gly Pro Gly Tyr Pro Ile Arg
    450                 455                 460

Ala Leu Val Gly Asp Glu Ala Glu Leu Pro Cys Arg Ile Ser Pro Gly
465                 470                 475                 480

Lys Asn Ala Thr Gly Met Glu Val Gly Trp Tyr Arg Ser Pro Phe Ser
                485                 490                 495

Arg Val Val His Leu Tyr Arg Asn Gly Lys Asp Gln Asp Ala Glu Gln
            500                 505                 510

Ala Pro Glu Tyr Arg Gly Arg Thr Glu Leu Leu Lys Glu Thr Ile Ser
        515                 520                 525

Glu Gly Lys Val Thr Leu Arg Ile Gln Asn Val Arg Phe Ser Asp Glu
    530                 535                 540

Gly Gly Tyr Thr Cys Phe Phe Arg Asp His Ser Tyr Gln Glu Glu Ala
545                 550                 555                 560

Ala Met Glu Leu Lys Val Glu Asp
                565


<210> SEQ ID NO 17
<211> LENGTH: 1338
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

gaggtgcagc tggtgcagtc cggcgccgag gtgaagaagc ccggcgcctc cgtgaaggtg     60

tcctgcaagg cctccggcta caccttcacc tcctactgga tgcactgggt gcggcaggcc    120

cccggccagc ggctggagtg gatcggcgag atcaacccca ccaacggccg gaccaactac    180

atcgagaagt tcaagtcccg ggccaccctg accgtggaca agtccgcctc caccgcctac    240

atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgc ccggggcacc    300

cgggcctacc actactgggg ccagggcacc atggtgaccg tgtcctccgc ctccaccaag    360

ggcccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc    420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc    480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc    540

ctcagcagcg tggtgactgt gccctccagc agcttgggca cccagaccta catctgcaac    600

gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttgagcccaa atcttgtgac    660

aaaactcaca catgcccacc gtgcccagca cctgaactcc tgggggggacc gtcagtcttc    720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacatgc    780

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc    840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt    900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc    960

aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa agccaaaggg   1020

cagccccgag aaccacaggt gtacaccctg cccccatccc gggatgagct gaccaagaac   1080

caggtccacc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg   1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac   1200

ggctccttcg ccctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac   1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   1320
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tccctgtctc cgggtaaa 1338

<210> SEQ ID NO 18
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

Glu 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

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

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
50 55 60

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

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

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

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

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

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

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

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

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

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225 230 235 240

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

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

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

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

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

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

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

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val His Leu Thr Cys Leu Val
355 360 365

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

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

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

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

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


<210> SEQ ID NO 19
<211> LENGTH: 639
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

gacatccaga tgacccagtc cccctcctcc ctgtccgcct ccgtgggcga ccgggtgacc     60

atcacctgcc gggcctccga caacctgtac tccaacctgg cctggtacca gcagaagccc    120

ggcaagtccc ccaagctgct ggtgtacgac gccaccaacc tggccgacgg cgtgccctcc    180

cggttctccg gctccggctc cggcaccgac tacaccctga ccatctcctc cctgcagccc    240

gaggacttcg ccacctacta ctgccagcac ttctggggca ccccctgac cttcggccag    300

ggcaccaagg tggagatcaa gactgtggct gcaccatctg tcttcatctt cccgccatct    360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc    420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag    480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg    540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg    600

agttcgcccg tcacaaagag cttcaacagg ggagagtgt                            639


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

<400> SEQUENCE: 20

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

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

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

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

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

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

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140
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Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

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

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

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

Asn Arg Gly Glu Cys
    210
```

<210> SEQ ID NO 21
<211> LENGTH: 1704
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

```
gaggtgcagc tggtgcagtc cggcgccgag gtgaagaagc ccggcgcctc cgtgaaggtg     60

tcctgcaagg cctccggcta caccttcacc tcctactgga tgcactgggt gcggcaggcc    120

cccggccagc ggctggagtg gatcggcgag atcaacccca ccaacggccg gaccaactac    180

atcgagaagt tcaagtcccg ggccaccctg accgtggaca agtccgcctc caccgcctac    240

atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgc ccggggcacc    300

cgggcctacc actactgggg ccagggcacc atggtgaccg tgtcctccgc ctccaccaag    360

ggcccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc    420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc    480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc    540

ctcagcagcg tggtgactgt gccctccagc agcttgggca cccagaccta catctgcaac    600

gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttgagcccaa atcttgtgac    660

aaaactcaca catgcccacc gtgcccagca cctgaactcc tgaggggacc gtcagtcttc    720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacatgc    780

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc    840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt    900

gtggtcagcg tccttaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc    960

aaggtctcca acaaagcccg cccagccccc atcgagaaaa ccatctccaa agccaaaggg   1020

cagccccgag aaccacaggt gaccaccctg cccccatccc gggatgagct gaccaagaac   1080

caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg   1140

gagagcaatg ggcagccgga gaacaactac aagaccttcc ctcccgtgct ggactccgac   1200

ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac   1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   1320

tccctgtctc cgggtaaagg aggcggtgga tcaggacaat tcagagtgat aggaccaggg   1380

tatcccatcc gggctttagt tggggatgaa gcagagctgc cgtgccgcat ctctcctggg   1440

aaaaatgcca cgggcatgga ggtgggttgg taccgttctc ccttctcaag agtggttcac   1500

ctctaccgaa atggcaagga ccaagatgca gagcaagcac ctgaataccg gggacgcaca   1560

gagcttctga aagagactat cagtgaggga aaggttaccc ttaggattca gaacgtgaga   1620

ttctcagatg aaggaggcta cacctgcttc ttcagagacc actcttacca agaagaggca   1680
```

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gcaatggagt tgaaagtgga agat 1704

<210> SEQ ID NO 22
<211> LENGTH: 568
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Glu 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

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

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
50 55 60

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

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

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

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

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

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

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

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

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

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
210 215 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Arg Gly Pro Ser Val Phe
225 230 235 240

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

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

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

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

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

Lys Val Ser Asn Lys Ala Arg Pro Ala Pro Ile Glu Lys Thr Ile Ser
325 330 335

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

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
355 360 365

-continued

```
Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

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

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

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

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

Gly Gly Ser Gly Gln Phe Arg Val Ile Gly Pro Gly Tyr Pro Ile Arg
    450                 455                 460

Ala Leu Val Gly Asp Glu Ala Glu Leu Pro Cys Arg Ile Ser Pro Gly
465                 470                 475                 480

Lys Asn Ala Thr Gly Met Glu Val Gly Trp Tyr Arg Ser Pro Phe Ser
                485                 490                 495

Arg Val Val His Leu Tyr Arg Asn Gly Lys Asp Gln Asp Ala Glu Gln
            500                 505                 510

Ala Pro Glu Tyr Arg Gly Arg Thr Glu Leu Leu Lys Glu Thr Ile Ser
        515                 520                 525

Glu Gly Lys Val Thr Leu Arg Ile Gln Asn Val Arg Phe Ser Asp Glu
    530                 535                 540

Gly Gly Tyr Thr Cys Phe Phe Arg Asp His Ser Tyr Gln Glu Glu Ala
545                 550                 555                 560

Ala Met Glu Leu Lys Val Glu Asp
                565
```

<210> SEQ ID NO 23
<211> LENGTH: 1338
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

```
gaggtgcagc tggtgcagtc cggcgccgag gtgaagaagc ccggcgcctc cgtgaaggtg     60

tcctgcaagg cctccggcta caccttcacc tcctactgga tgcactgggt gcggcaggcc    120

cccggccagc ggctggagtg gatcggcgag atcaacccca ccaacggccg gaccaactac    180

atcgagaagt tcaagtcccg ggccaccctg accgtggaca agtccgcctc caccgcctac    240

atggagctgt cctccctgcg gtccgaggac accgccgtgt actactgcgc ccggggcacc    300

cgggcctacc actactgggg ccagggcacc atggtgaccg tgtcctccgc ctccaccaag    360

ggcccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc    420

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc    480

gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc    540

ctcagcagcg tggtgactgt gccctccagc agcttgggca cccagaccta catctgcaac    600

gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttgagcccaa atcttgtgac    660

aaaactcaca catgcccacc gtgcccagca cctgaactcc tgaggggacc gtcagtcttc    720

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga ggtcacatgc    780

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc    840

gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag cacgtaccgt    900

gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga gtacaagtgc    960
```

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```
aaggtctcca acaaagcccg cccagccccc atcgagaaaa ccatctccaa agccaaaggg   1020

cagccccgag aaccacaggt gtacaccctg cccccatccc gggatgagct gaccaagaac   1080

caggtccacc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc cgtggagtgg   1140

gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct ggactccgac   1200

ggctccttcg ccctctacag caagctcacc gtggacaaga gcaggtggca gcaggggaac   1260

gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc   1320

tccctgtctc cgggtaaa                                                1338
```

<210> SEQ ID NO 24
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

```
Glu 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

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

Gly Glu Ile Asn Pro Thr Asn Gly Arg Thr Asn Tyr Ile Glu Lys Phe
    50                  55                  60

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

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

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

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

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

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

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

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

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

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Arg Gly Pro Ser Val Phe
225                 230                 235                 240

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

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

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

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

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```
Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Arg Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

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

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val His Leu Thr Cys Leu Val
        355                 360                 365

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

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

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

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

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


<210> SEQ ID NO 25
<211> LENGTH: 2601
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

acccaagtgt gcaccggcac agacatgaag ctgcggctcc ctgccagtcc cgagacccac     60

ctggacatgc tccgccacct ctaccagggc tgccaggtgg tgcagggaaa cctggaactc    120

acctacctgc ccaccaatgc cagcctgtcc ttcctgcagg atatccagga ggtgcagggc    180

tacgtgctca tcgctcacaa ccaagtgagg caggtcccac tgcagaggct gcggattgtg    240

cgaggcaccc agctctttga ggacaactat gccctggccg tgctagacaa tggagacccg    300

ctgaacaata ccacccctgt cacaggggcc tccccaggag gcctgcggga gctgcagctt    360

cgaagcctca cagagatctt gaaaggaggg gtcttgatcc agcggaaccc ccagctctgc    420

taccaggaca cgattttgtg gaaggacatc ttccacaaga acaaccagct ggctctcaca    480

ctgatagaca ccaaccgctc tcgggcctgc cacccctgtt ctccgatgtg taagggctcc    540

cgctgctggg gagagagttc tgaggattgt cagagcctga cgcgcactgt ctgtgccggt    600

ggctgtgccc gctgcaaggg gccactgccc actgactgct gccatgagca gtgtgctgcc    660

ggctgcacgg gccccaagca ctctgactgc ctggcctgcc tccacttcaa ccacagtggc    720

atctgtgagc tgcactgccc agccctggtc acctacaaca cagacacgtt tgagtccatg    780

cccaatcccg agggccggta tacattcggc gccagctgtg tgactgcctg tccctacaac    840

tacctttcta cggacgtggg atcctgcacc ctcgtctgcc ccctgcacaa ccaagaggtg    900

acagcagagg atggaacaca gcggtgtgag aagtgcagca agccctgtgc ccgagtgtgc    960

tatggtctgg gcatggagca cttgcgagag gtgagggcag ttaccagtgc caatatccag   1020

gagtttgctg gctgcaagaa gatctttggg agcctggcat ttctgccgga gagctttgat   1080

ggggacccag cctccaacac tgccccgctc cagccagagc agctccaagt gtttgagact   1140

ctggaagaga tcacaggtta cctatacatc tcagcatggc cggacagcct gcctgacctc   1200

agcgtcttcc agaacctgca agtaatccgg ggacgaattc tgcacaatgg cgcctactcg   1260

ctgaccctgc aagggctggg catcagctgg ctggggctgc gctcactgag ggaactgggc   1320
```

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```
agtggactgg ccctcatcca ccataacacc cacctctgct tcgtgcacac ggtgccctgg   1380

gaccagctct ttcggaaccc gcaccaagct ctgctccaca ctgccaaccg gccagaggac   1440

gagtgtgtgg gcgagggcct ggcctgccac cagctgtgcg cccgagggca ctgctggggt   1500

ccagggccca cccagtgtgt caactgcagc cagttccttc ggggccagga gtgcgtggag   1560

gaatgccgag tactgcaggg gctccccagg gagtatgtga atgccaggca ctgtttgccg   1620

tgccaccctg agtgtcagcc ccagaatggc tcagtgacct gttttggacc ggaggctgac   1680

cagtgtgtgg cctgtgccca ctataaggac cctcccttct gcgtggcccg ctgccccagc   1740

ggtgtgaaac ctgacctctc ctacatgccc atctggaagt ttccagatga ggagggcgca   1800

tgccagcctt gccccatcaa ctgcacccac tcctgtgtgg acctggatga caagggctgc   1860

cccgccgagc agagagccag ccctctgacg attgaaggcc gcatggatcc caaatcttct   1920

gacaaaactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc   1980

ttcctcttcc ccccaaaacc caaggacacc ctctacatca ctcgggaacc tgaggtcaca   2040

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac   2100

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac   2160

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag   2220

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa   2280

gggcagcccc gagaaccaca ggtgaccacc ctgcccccat cccgggatga gctgaccaag   2340

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag   2400

tgggagagca atgggcagcc ggagaacaac tacaagacct tccctcccgt gctggactcc   2460

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg   2520

aacgtcttct catgctctgt gatgcatgag gctctgaaat tccactacac gcagaagagc   2580

ctctccctgt ctcctggtaa a                                             2601
```

<210> SEQ ID NO 26
<211> LENGTH: 867
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

```
Thr Gln Val Cys Thr Gly Thr Asp Met Lys Leu Arg Leu Pro Ala Ser
1               5                  10                  15

Pro Glu Thr His Leu Asp Met Leu Arg His Leu Tyr Gln Gly Cys Gln
            20                  25                  30

Val Val Gln Gly Asn Leu Glu Leu Thr Tyr Leu Pro Thr Asn Ala Ser
        35                  40                  45

Leu Ser Phe Leu Gln Asp Ile Gln Glu Val Gln Gly Tyr Val Leu Ile
    50                  55                  60

Ala His Asn Gln Val Arg Gln Val Pro Leu Gln Arg Leu Arg Ile Val
65                  70                  75                  80

Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr Ala Leu Ala Val Leu Asp
                85                  90                  95

Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro Val Thr Gly Ala Ser Pro
            100                 105                 110

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

Gly Gly Val Leu Ile Gln Arg Asn Pro Gln Leu Cys Tyr Gln Asp Thr
    130                 135                 140
```

-continued

```
Ile Leu Trp Lys Asp Ile Phe His Lys Asn Asn Gln Leu Ala Leu Thr
145                 150                 155                 160

Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys His Pro Cys Ser Pro Met
                165                 170                 175

Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser Ser Glu Asp Cys Gln Ser
            180                 185                 190

Leu Thr Arg Thr Val Cys Ala Gly Gly Cys Ala Arg Cys Lys Gly Pro
        195                 200                 205

Leu Pro Thr Asp Cys Cys His Glu Gln Cys Ala Ala Gly Cys Thr Gly
    210                 215                 220

Pro Lys His Ser Asp Cys Leu Ala Cys Leu His Phe Asn His Ser Gly
225                 230                 235                 240

Ile Cys Glu Leu His Cys Pro Ala Leu Val Thr Tyr Asn Thr Asp Thr
                245                 250                 255

Phe Glu Ser Met Pro Asn Pro Glu Gly Arg Tyr Thr Phe Gly Ala Ser
            260                 265                 270

Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu Ser Thr Asp Val Gly Ser
        275                 280                 285

Cys Thr Leu Val Cys Pro Leu His Asn Gln Glu Val Thr Ala Glu Asp
    290                 295                 300

Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys Pro Cys Ala Arg Val Cys
305                 310                 315                 320

Tyr Gly Leu Gly Met Glu His Leu Arg Glu Val Arg Ala Val Thr Ser
                325                 330                 335

Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys Lys Ile Phe Gly Ser Leu
            340                 345                 350

Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp Pro Ala Ser Asn Thr Ala
        355                 360                 365

Pro Leu Gln Pro Glu Gln Leu Gln Val Phe Glu Thr Leu Glu Glu Ile
    370                 375                 380

Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro Asp Ser Leu Pro Asp Leu
385                 390                 395                 400

Ser Val Phe Gln Asn Leu Gln Val Ile Arg Gly Arg Ile Leu His Asn
                405                 410                 415

Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu Gly Ile Ser Trp Leu Gly
            420                 425                 430

Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly Leu Ala Leu Ile His His
        435                 440                 445

Asn Thr His Leu Cys Phe Val His Thr Val Pro Trp Asp Gln Leu Phe
    450                 455                 460

Arg Asn Pro His Gln Ala Leu Leu His Thr Ala Asn Arg Pro Glu Asp
465                 470                 475                 480

Glu Cys Val Gly Glu Gly Leu Ala Cys His Gln Leu Cys Ala Arg Gly
                485                 490                 495

His Cys Trp Gly Pro Gly Pro Thr Gln Cys Val Asn Cys Ser Gln Phe
            500                 505                 510

Leu Arg Gly Gln Glu Cys Val Glu Glu Cys Arg Val Leu Gln Gly Leu
        515                 520                 525

Pro Arg Glu Tyr Val Asn Ala Arg His Cys Leu Pro Cys His Pro Glu
    530                 535                 540

Cys Gln Pro Gln Asn Gly Ser Val Thr Cys Phe Gly Pro Glu Ala Asp
545                 550                 555                 560
```

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```
Gln Cys Val Ala Cys Ala His Tyr Lys Asp Pro Pro Phe Cys Val Ala
                565                 570                 575

Arg Cys Pro Ser Gly Val Lys Pro Asp Leu Ser Tyr Met Pro Ile Trp
            580                 585                 590

Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln Pro Cys Pro Ile Asn Cys
        595                 600                 605

Thr His Ser Cys Val Asp Leu Asp Asp Lys Gly Cys Pro Ala Glu Gln
    610                 615                 620

Arg Ala Ser Pro Leu Thr Ile Glu Gly Arg Met Asp Pro Lys Ser Ser
625                 630                 635                 640

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
                645                 650                 655

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr
            660                 665                 670

Ile Thr Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
        675                 680                 685

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
    690                 695                 700

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
705                 710                 715                 720

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
                725                 730                 735

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
            740                 745                 750

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
        755                 760                 765

Thr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
    770                 775                 780

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
785                 790                 795                 800

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Phe Pro Pro
                805                 810                 815

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
            820                 825                 830

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
        835                 840                 845

His Glu Ala Leu Lys Phe His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
    850                 855                 860

Pro Gly Lys
865
```

<210> SEQ ID NO 27
<211> LENGTH: 699
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

```
gttgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaactc     60

ctggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct ctacatcact    120

cgggaacctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag    180

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag    240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg    300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa    360
```

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accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc 420

cgggatgagc tgaccaagaa ccaggtccac ctgacctgcc tggtcaaagg cttctatccc 480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 540

cctcccgtgc tggactccga cggctccttc gccctctaca gcaagctcac cgtggacaag 600

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgaaattc 660

cactacacgc agaagagcct ctccctgtct ccgggtaaa 699

<210> SEQ ID NO 28
<211> LENGTH: 233
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
20 25 30

Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys Val
35 40 45

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

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65 70 75 80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
85 90 95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
100 105 110

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

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
130 135 140

Thr Lys Asn Gln Val His Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145 150 155 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
165 170 175

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Ala Leu
180 185 190

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
195 200 205

Phe Ser Cys Ser Val Met His Glu Ala Leu Lys Phe His Tyr Thr Gln
210 215 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys
225 230

<210> SEQ ID NO 29
<211> LENGTH: 2835
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

gttgagccca aatcttctga caaaactcac acatgcccac cgtgcccagc acctgaactc 60

ctgaggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct ctacatcact 120

cgggaacctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 180

-continued

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 240

cagtacaaca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 300

aatggcaagg agtacaagtg caaggtctcc aacaaagccc gcccagcccc catcgagaaa 360

accatctcca aagccaaagg gcagccccga gaaccacagg tgaccaccct gcccccatcc 420

cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 480

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccttc 540

cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag 600

agcaggtggc agcaggggaa cgtcttctca tgctctgtga tgcatgaggc tctgaaattc 660

cactacacgc agaagagcct ctccctgtct ccgggtaaag gaggcggtgg atcaaaatcc 720

tccaatgaag ctactaacat tactccaaag cataatatga aagcattttt ggatgaattg 780

aaagctgaga acatcaagaa gttcttatat aattttacac agataccaca tttagcagga 840

acagaacaaa actttcagct tgcaaagcaa attcaatccc agtggaaaga atttggcctg 900

gattctgttg agctagcaca ttatgatgtc ctgttgtcct acccaaataa gactcatccc 960

aactacatct caataattaa tgaagatgga aatgagattt tcaacacatc attatttgaa 1020

ccacctcctc caggatatga aaatgtttcg gatattgtac caccttcag tgctttctct 1080

cctcaaggaa tgccagaggg cgatctagtg tatgttaact atgcacgaac tgaagacttc 1140

tttaaattgg aacgggacat gaaaatcaat tgctctggga aaattgtaat tgccagatat 1200

gggaaagttt tcagaggaaa taaggttaaa aatgcccagc tggcaggggc caaaggagtc 1260

attctctact ccgaccctgc tgactacttt gctcctgggg tgaagtccta tccagatggt 1320

tggaatcttc ctggaggtgg tgtccagcgt ggaaatatcc taaatctgaa tggtgcagga 1380

gaccctctca caccaggtta cccagcaaat gaatatgctt ataggcgtgg aattgcagag 1440

gctgttggtc ttccaagtat tcctgttcat ccaattggat actatgatgc acagaagctc 1500

ctagaaaaaa tgggtggctc agcaccacca gatagcagct ggagaggaag tctcaaagtg 1560

ccctacaatg ttggacctgg ctttactgga aacttttcta cacaaaaagt caagatgcac 1620

atccactcta ccaatgaagt gacaagaatt tacaatgtga taggtactct cagaggagca 1680

gtggaaccag acagatatgt cattctggga ggtcaccggg actcatgggt gtttggtggt 1740

attgaccctc agagtggagc agctgttgtt catgaaattg tgaggagctt tggaacactg 1800

aaaaaggaag ggtggagacc tagaagaaca attttgtttg caagctggga tgcagaagaa 1860

tttggtcttc ttggttctac tgagtgggca gaggagaatt caagactcct tcaagagcgt 1920

ggcgtggctt atattaatgc tgactcatct atagaaggaa actacactct gagagttgat 1980

tgtacaccgc tgatgtacag cttggtacac aacctaacaa aagagctgaa aagccctgat 2040

gaaggctttg aaggcaaatc tctttatgaa agttggacta aaaaaagtcc ttccccagag 2100

ttcagtggca tgcccaggat aagcaaattg ggatctggaa atgattttga ggtgttcttc 2160

caacgacttg gaattgcttc aggcagagca cggtatacta aaaattggga aacaaacaaa 2220

ttcagcggct atccactgta tcacagtgtc tatgaaacat atgagttggt ggaaaagttt 2280

tatgatccaa tgtttaaata tcacctcact gtggcccagg ttcgaggagg gatggtgttt 2340

gagctagcca attccatagt gctccctttt gattgtcgag attatgctgt agttttaaga 2400

aagtatgctg acaaaatcta cagtatttct atgaaacatc cacaggaaat gaagacatac 2460

agtgtatcat ttgattcact tttttctgca gtaaagaatt ttacagaaat tgcttccaag 2520

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```
ttcagtgaga gactccagga ctttgacaaa agcaacccaa tagtattaag aatgatgaat   2580

gatcaactca tgtttctgga aagagcattt attgatccat tagggttacc agacaggcct   2640

ttttataggc atgtcatcta tgctccaagc agccacaaca agtatgcagg ggagtcattc   2700

ccaggaattt atgatgctct gtttgatatt gaaagcaaag tggacccttc caaggcctgg   2760

ggagaagtga agagacagat ttatgttgca gccttcacag tgcaggcagc tgcagagact   2820

ttgagtgaag tagcc                                                    2835
```

<210> SEQ ID NO 30
<211> LENGTH: 945
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

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

Ala Pro Glu Leu Leu Arg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            20                  25                  30

Pro Lys Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys Val
        35                  40                  45

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

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
65                  70                  75                  80

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                85                  90                  95

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
            100                 105                 110

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

Pro Arg Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    130                 135                 140

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
145                 150                 155                 160

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                165                 170                 175

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

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        195                 200                 205

Phe Ser Cys Ser Val Met His Glu Ala Leu Lys Phe His Tyr Thr Gln
    210                 215                 220

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Lys Ser
225                 230                 235                 240

Ser Asn Glu Ala Thr Asn Ile Thr Pro Lys His Asn Met Lys Ala Phe
                245                 250                 255

Leu Asp Glu Leu Lys Ala Glu Asn Ile Lys Lys Phe Leu Tyr Asn Phe
            260                 265                 270

Thr Gln Ile Pro His Leu Ala Gly Thr Glu Gln Asn Phe Gln Leu Ala
        275                 280                 285

Lys Gln Ile Gln Ser Gln Trp Lys Glu Phe Gly Leu Asp Ser Val Glu
    290                 295                 300

Leu Ala His Tyr Asp Val Leu Leu Ser Tyr Pro Asn Lys Thr His Pro
305                 310                 315                 320
```

-continued

```
Asn Tyr Ile Ser Ile Ile Asn Glu Asp Gly Asn Glu Ile Phe Asn Thr
                325                 330                 335

Ser Leu Phe Glu Pro Pro Pro Pro Gly Tyr Glu Asn Val Ser Asp Ile
            340                 345                 350

Val Pro Pro Phe Ser Ala Phe Ser Pro Gln Gly Met Pro Glu Gly Asp
        355                 360                 365

Leu Val Tyr Val Asn Tyr Ala Arg Thr Glu Asp Phe Phe Lys Leu Glu
    370                 375                 380

Arg Asp Met Lys Ile Asn Cys Ser Gly Lys Ile Val Ile Ala Arg Tyr
385                 390                 395                 400

Gly Lys Val Phe Arg Gly Asn Lys Val Lys Asn Ala Gln Leu Ala Gly
                405                 410                 415

Ala Lys Gly Val Ile Leu Tyr Ser Asp Pro Ala Asp Tyr Phe Ala Pro
            420                 425                 430

Gly Val Lys Ser Tyr Pro Asp Gly Trp Asn Leu Pro Gly Gly Gly Val
        435                 440                 445

Gln Arg Gly Asn Ile Leu Asn Leu Asn Gly Ala Gly Asp Pro Leu Thr
    450                 455                 460

Pro Gly Tyr Pro Ala Asn Glu Tyr Ala Tyr Arg Arg Gly Ile Ala Glu
465                 470                 475                 480

Ala Val Gly Leu Pro Ser Ile Pro Val His Pro Ile Gly Tyr Tyr Asp
                485                 490                 495

Ala Gln Lys Leu Leu Glu Lys Met Gly Gly Ser Ala Pro Pro Asp Ser
            500                 505                 510

Ser Trp Arg Gly Ser Leu Lys Val Pro Tyr Asn Val Gly Pro Gly Phe
        515                 520                 525

Thr Gly Asn Phe Ser Thr Gln Lys Val Lys Met His Ile His Ser Thr
    530                 535                 540

Asn Glu Val Thr Arg Ile Tyr Asn Val Ile Gly Thr Leu Arg Gly Ala
545                 550                 555                 560

Val Glu Pro Asp Arg Tyr Val Ile Leu Gly Gly His Arg Asp Ser Trp
                565                 570                 575

Val Phe Gly Gly Ile Asp Pro Gln Ser Gly Ala Ala Val Val His Glu
            580                 585                 590

Ile Val Arg Ser Phe Gly Thr Leu Lys Lys Glu Gly Trp Arg Pro Arg
        595                 600                 605

Arg Thr Ile Leu Phe Ala Ser Trp Asp Ala Glu Glu Phe Gly Leu Leu
    610                 615                 620

Gly Ser Thr Glu Trp Ala Glu Glu Asn Ser Arg Leu Leu Gln Glu Arg
625                 630                 635                 640

Gly Val Ala Tyr Ile Asn Ala Asp Ser Ser Ile Glu Gly Asn Tyr Thr
                645                 650                 655

Leu Arg Val Asp Cys Thr Pro Leu Met Tyr Ser Leu Val His Asn Leu
            660                 665                 670

Thr Lys Glu Leu Lys Ser Pro Asp Glu Gly Phe Glu Gly Lys Ser Leu
        675                 680                 685

Tyr Glu Ser Trp Thr Lys Lys Ser Pro Ser Pro Glu Phe Ser Gly Met
    690                 695                 700

Pro Arg Ile Ser Lys Leu Gly Ser Gly Asn Asp Phe Glu Val Phe Phe
705                 710                 715                 720

Gln Arg Leu Gly Ile Ala Ser Gly Arg Ala Arg Tyr Thr Lys Asn Trp
                725                 730                 735
```

-continued

```
Glu Thr Asn Lys Phe Ser Gly Tyr Pro Leu Tyr His Ser Val Tyr Glu
            740                 745                 750

Thr Tyr Glu Leu Val Glu Lys Phe Tyr Asp Pro Met Phe Lys Tyr His
        755                 760                 765

Leu Thr Val Ala Gln Val Arg Gly Gly Met Val Phe Glu Leu Ala Asn
    770                 775                 780

Ser Ile Val Leu Pro Phe Asp Cys Arg Asp Tyr Ala Val Val Leu Arg
785                 790                 795                 800

Lys Tyr Ala Asp Lys Ile Tyr Ser Ile Ser Met Lys His Pro Gln Glu
                805                 810                 815

Met Lys Thr Tyr Ser Val Ser Phe Asp Ser Leu Phe Ser Ala Val Lys
            820                 825                 830

Asn Phe Thr Glu Ile Ala Ser Lys Phe Ser Glu Arg Leu Gln Asp Phe
        835                 840                 845

Asp Lys Ser Asn Pro Ile Val Leu Arg Met Met Asn Asp Gln Leu Met
    850                 855                 860

Phe Leu Glu Arg Ala Phe Ile Asp Pro Leu Gly Leu Pro Asp Arg Pro
865                 870                 875                 880

Phe Tyr Arg His Val Ile Tyr Ala Pro Ser Ser His Asn Lys Tyr Ala
                885                 890                 895

Gly Glu Ser Phe Pro Gly Ile Tyr Asp Ala Leu Phe Asp Ile Glu Ser
            900                 905                 910

Lys Val Asp Pro Ser Lys Ala Trp Gly Glu Val Lys Arg Gln Ile Tyr
        915                 920                 925

Val Ala Ala Phe Thr Val Gln Ala Ala Ala Glu Thr Leu Ser Glu Val
    930                 935                 940

Ala
945
```

<210> SEQ ID NO 31
<211> LENGTH: 2469
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

```
atggcatctc cgggctctgg cttttggtct ttcgggtcgg aagatggctc tggggattcc     60

gagaatcccg gcacagcgcg agcctggtgc caagtggctc agaagttcac gggcggcatc    120

ggaaacaaac tgtgcgccct gctctacgga gacgccgaga agccggcgga gagcggcggg    180

agccaacccc cgcgggccgc cgcccggaag gccgcctgcg cctgcgacca gaagccctgc    240

agctgctcca aagtggatgt caactacgcg tttctccatg caacagacct gctgccggcg    300

tgtgatggag aaaggcccac tttggcgttt ctgcaagatg ttatgaacat tttacttcag    360

tatgtggtga aaagtttcga tagatcaacc aaagtgattg atttccatta tcctaatgag    420

cttctccaag aatataattg ggaattggca gaccaaccac aaaatttgga ggaaattttg    480

atgcattgcc aaacaactct aaaatatgca attaaaacag ggcatcctag atacttcaat    540

caactttcta ctggtttgga tatggttgga ttagcagcag actggctgac atcaacagca    600

aatactaaca tgttcaccta tgaaattgct ccagtatttg tgcttttgga atatgtcaca    660

ctaaagaaaa tgagagaaat cattggctgg ccaggggget ctggcgatgg gatattttct    720

cccggtggcg ccatatctaa catgtatgcc atgatgatcg cacgctttaa gatgttccca    780

gaagtcaagg agaaaggaat ggctgctctt cccaggctca ttgccttcac gtctgaacat    840

agtcattttt ctctcaagaa gggagctgca gccttaggga ttggaacaga cagcgtgatt    900
```

-continued

```
ctgattaaat gtgatgagag agggaaaatg attccatctg atcttgaaag aaggattctt    960

gaagccaaac agaaagggtt tgttcctttc ctcgtgagtg ccacagctgg aaccaccgtg   1020

tacggagcat ttgacccccc cttagctgtc gctgacattt gcaaaaagta taagatctgg   1080

atgcatgtgg atgcagcttg gggtggggga ttactgatgt cccgaaaaca caagtggaaa   1140

ctgagtggcg tggagagggc caactctgtg acgtggaatc cacacaagat gatgggagtc   1200

cctttgcagt gctctgctct cctggttaga gaagagggat tgatgcagaa ttgcaaccaa   1260

atgcatgcct cctacctctt tcagcaagat aaacattatg acctgtccta tgacactgga   1320

gacaaggcct tacagtgcgg acgccacgtt gatgttttta aactatggct gatgtggagg   1380

gcaaagggga ctaccgggtt tgaagcgcat gttgataaat gtttggagtt ggcagagtat   1440

ttatacaaca tcataaaaaa ccgagaagga tatgagatgg tgtttgatgg gaagcctcag   1500

cacacaaatg tctgcttctg gtacattcct ccaagcttgc gtactctgga agacaatgaa   1560

gagagaatga gtcgcctctc gaaggtggct ccagtgatta aagccagaat gatggagtat   1620

ggaaccacaa tggtcagcta ccaacccttg ggagacaagg tcaatttctt ccgcatggtc   1680

atctcaaacc cagcggcaac tcaccaagac attgacttcc tgattgaaga aatagaacgc   1740

cttggacaag atttaggagg cggtggatca gttgagccca aatcttctga caaaactcac   1800

acatgcccac cgtgcccagc acctgaactc ctgaggggac cgtcagtctt cctcttcccc   1860

ccaaaaccca aggacaccct ctacatcact cgggaacctg aggtcacatg cgtggtggtg   1920

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg   1980

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc   2040

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc   2100

aacaaagccc gcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga   2160

gaaccacagg tgaccaccct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc   2220

ctgacctgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat   2280

gggcagccgg agaacaacta caagaccttc cctcccgtgc tggactccga cggctccttc   2340

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca   2400

tgctctgtga tgcatgaggc tctgaaattc cactacacgc agaagagcct ctccctgtct   2460

ccgggtaaa                                                           2469
```

<210> SEQ ID NO 32
<211> LENGTH: 823
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

```
Met Ala Ser Pro Gly Ser Gly Phe Trp Ser Phe Gly Ser Glu Asp Gly
1               5                  10                  15

Ser Gly Asp Ser Glu Asn Pro Gly Thr Ala Arg Ala Trp Cys Gln Val
            20                  25                  30

Ala Gln Lys Phe Thr Gly Gly Ile Gly Asn Lys Leu Cys Ala Leu Leu
        35                  40                  45

Tyr Gly Asp Ala Glu Lys Pro Ala Glu Ser Gly Gly Ser Gln Pro Pro
    50                  55                  60

Arg Ala Ala Ala Arg Lys Ala Ala Cys Ala Cys Asp Gln Lys Pro Cys
65                  70                  75                  80

Ser Cys Ser Lys Val Asp Val Asn Tyr Ala Phe Leu His Ala Thr Asp
```

-continued

```
               85                  90                  95

Leu Leu Pro Ala Cys Asp Gly Glu Arg Pro Thr Leu Ala Phe Leu Gln
            100                 105                 110

Asp Val Met Asn Ile Leu Leu Gln Tyr Val Val Lys Ser Phe Asp Arg
        115                 120                 125

Ser Thr Lys Val Ile Asp Phe His Tyr Pro Asn Glu Leu Leu Gln Glu
    130                 135                 140

Tyr Asn Trp Glu Leu Ala Asp Gln Pro Gln Asn Leu Glu Glu Ile Leu
145                 150                 155                 160

Met His Cys Gln Thr Thr Leu Lys Tyr Ala Ile Lys Thr Gly His Pro
                165                 170                 175

Arg Tyr Phe Asn Gln Leu Ser Thr Gly Leu Asp Met Val Gly Leu Ala
            180                 185                 190

Ala Asp Trp Leu Thr Ser Thr Ala Asn Thr Asn Met Phe Thr Tyr Glu
        195                 200                 205

Ile Ala Pro Val Phe Val Leu Leu Glu Tyr Val Thr Leu Lys Lys Met
    210                 215                 220

Arg Glu Ile Ile Gly Trp Pro Gly Gly Ser Gly Asp Gly Ile Phe Ser
225                 230                 235                 240

Pro Gly Gly Ala Ile Ser Asn Met Tyr Ala Met Met Ile Ala Arg Phe
                245                 250                 255

Lys Met Phe Pro Glu Val Lys Glu Lys Gly Met Ala Ala Leu Pro Arg
            260                 265                 270

Leu Ile Ala Phe Thr Ser Glu His Ser His Phe Ser Leu Lys Lys Gly
        275                 280                 285

Ala Ala Ala Leu Gly Ile Gly Thr Asp Ser Val Ile Leu Ile Lys Cys
    290                 295                 300

Asp Glu Arg Gly Lys Met Ile Pro Ser Asp Leu Glu Arg Arg Ile Leu
305                 310                 315                 320

Glu Ala Lys Gln Lys Gly Phe Val Pro Phe Leu Val Ser Ala Thr Ala
                325                 330                 335

Gly Thr Thr Val Tyr Gly Ala Phe Asp Pro Leu Leu Ala Val Ala Asp
            340                 345                 350

Ile Cys Lys Lys Tyr Lys Ile Trp Met His Val Asp Ala Ala Trp Gly
        355                 360                 365

Gly Gly Leu Leu Met Ser Arg Lys His Lys Trp Lys Leu Ser Gly Val
    370                 375                 380

Glu Arg Ala Asn Ser Val Thr Trp Asn Pro His Lys Met Met Gly Val
385                 390                 395                 400

Pro Leu Gln Cys Ser Ala Leu Leu Val Arg Glu Glu Gly Leu Met Gln
                405                 410                 415

Asn Cys Asn Gln Met His Ala Ser Tyr Leu Phe Gln Gln Asp Lys His
            420                 425                 430

Tyr Asp Leu Ser Tyr Asp Thr Gly Asp Lys Ala Leu Gln Cys Gly Arg
        435                 440                 445

His Val Asp Val Phe Lys Leu Trp Leu Met Trp Arg Ala Lys Gly Thr
    450                 455                 460

Thr Gly Phe Glu Ala His Val Asp Lys Cys Leu Glu Leu Ala Glu Tyr
465                 470                 475                 480

Leu Tyr Asn Ile Ile Lys Asn Arg Glu Gly Tyr Glu Met Val Phe Asp
                485                 490                 495

Gly Lys Pro Gln His Thr Asn Val Cys Phe Trp Tyr Ile Pro Pro Ser
            500                 505                 510
```

-continued

```
Leu Arg Thr Leu Glu Asp Asn Glu Glu Arg Met Ser Arg Leu Ser Lys
        515                 520                 525

Val Ala Pro Val Ile Lys Ala Arg Met Met Glu Tyr Gly Thr Thr Met
    530                 535                 540

Val Ser Tyr Gln Pro Leu Gly Asp Lys Val Asn Phe Phe Arg Met Val
545                 550                 555                 560

Ile Ser Asn Pro Ala Ala Thr His Gln Asp Ile Asp Phe Leu Ile Glu
                565                 570                 575

Glu Ile Glu Arg Leu Gly Gln Asp Leu Gly Gly Gly Gly Ser Val Glu
            580                 585                 590

Pro Lys Ser Ser Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
        595                 600                 605

Glu Leu Leu Arg Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
    610                 615                 620

Asp Thr Leu Tyr Ile Thr Arg Glu Pro Glu Val Thr Cys Val Val Val
625                 630                 635                 640

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
                645                 650                 655

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
            660                 665                 670

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
        675                 680                 685

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Arg
    690                 695                 700

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
705                 710                 715                 720

Glu Pro Gln Val Thr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
                725                 730                 735

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
            740                 745                 750

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
        755                 760                 765

Thr Phe Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
    770                 775                 780

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
785                 790                 795                 800

Cys Ser Val Met His Glu Ala Leu Lys Phe His Tyr Thr Gln Lys Ser
                805                 810                 815

Leu Ser Leu Ser Pro Gly Lys
            820


<210> SEQ ID NO 33
<211> LENGTH: 1683
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

atgagtgaca gacccacagc aaggcggtgg ggtaagtgtg gacctttgtg taccagagag     60

aacatcatgg tggctttcaa aggggtctgg actcaagctt tctggaaagc agtcacagcg    120

gaatttctgg ccatgcttat ttttgttctc ctcagcctgg gatccaccat caactggggt    180

ggaacagaaa agcctttacc ggtcgacatg gttctcatct ccctttgctt tggactcagc    240

attgcaacca tggtgcagtg ctttggccat atcagcggtg gccacatcaa ccctgcagtg    300
```

-continued

actgtggcca tggtgtgcac caggaagatc agcatcgcca agtctgtctt ctacatcgca 360

gcccagtgcc tgggggccat cattggagca ggaatcctct atctggtcac acctcccagt 420

gtggtgggag gcctgggagt caccatggtt catggaaatc ttaccgctgg tcatggtctc 480

ctggttgagt tgataatcac atttcaattg gtgtttacta tctttgccag ctgtgattcc 540

aaacggactg atgtcactgg ctcaatagct ttagcaattg gattttctgt tgcaattgga 600

catttatttg caatcaatta tactggtgcc agcatgaatc ccgcccgatc ctttggacct 660

gcagttatca tgggaaattg ggaaaaccat tggatatatt gggttgggcc catcatagga 720

gctgtcctcg ctggtggcct ttatgagtat gtcttctgtc cagatgttga attcaaacgt 780

cgttttaaag aagccttcag caaagctgcc cagcaaacaa aaggaagcta catggaggtg 840

gaggacaaca ggagtcaggt agagacggat gacctgattc taaaacctgg agtggtgcat 900

gtgattgacg ttgaccgggg agaggagaag aaggggaaag accaatctgg agaggtattg 960

tcttcagtag gaggcggtgg atcagttgag cccaaatctt ctgacaaaac tcacacatgc 1020

ccaccgtgcc cagcacctga actcctgagg ggaccgtcag tcttcctctt cccccaaaa 1080

cccaaggaca ccctctacat cactcgggaa cctgaggtca catgcgtggt ggtggacgtg 1140

agccacgaag accctgaggt caagttcaac tggtacgtgg acggcgtgga ggtgcataat 1200

gccaagacaa agccgcggga ggagcagtac aacagcacgt accgtgtggt cagcgtcctc 1260

accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaacaaa 1320

gcccgcccag cccccatcga gaaaaccatc tccaaagcca aagggcagcc ccgagaacca 1380

caggtgacca ccctgccccc atcccgggat gagctgacca agaaccaggt cagcctgacc 1440

tgcctggtca aaggcttcta tcccagcgac atcgccgtgg agtgggagag caatgggcag 1500

ccggagaaca actacaagac cttccctccc gtgctggact ccgacggctc cttcttcctc 1560

tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtctt ctcatgctct 1620

gtgatgcatg aggctctgaa attccactac acgcagaaga gcctctccct gtctccgggt 1680

aaa 1683

<210> SEQ ID NO 34
<211> LENGTH: 561
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Met Ser Asp Arg Pro Thr Ala Arg Arg Trp Gly Lys Cys Gly Pro Leu
1 5 10 15

Cys Thr Arg Glu Asn Ile Met Val Ala Phe Lys Gly Val Trp Thr Gln
20 25 30

Ala Phe Trp Lys Ala Val Thr Ala Glu Phe Leu Ala Met Leu Ile Phe
35 40 45

Val Leu Leu Ser Leu Gly Ser Thr Ile Asn Trp Gly Gly Thr Glu Lys
50 55 60

Pro Leu Pro Val Asp Met Val Leu Ile Ser Leu Cys Phe Gly Leu Ser
65 70 75 80

Ile Ala Thr Met Val Gln Cys Phe Gly His Ile Ser Gly Gly His Ile
85 90 95

Asn Pro Ala Val Thr Val Ala Met Val Cys Thr Arg Lys Ile Ser Ile
100 105 110

Ala Lys Ser Val Phe Tyr Ile Ala Ala Gln Cys Leu Gly Ala Ile Ile
115 120 125

-continued

```
Gly Ala Gly Ile Leu Tyr Leu Val Thr Pro Pro Ser Val Val Gly Gly
    130                 135                 140

Leu Gly Val Thr Met Val His Gly Asn Leu Thr Ala Gly His Gly Leu
145                 150                 155                 160

Leu Val Glu Leu Ile Ile Thr Phe Gln Leu Val Phe Thr Ile Phe Ala
                165                 170                 175

Ser Cys Asp Ser Lys Arg Thr Asp Val Thr Gly Ser Ile Ala Leu Ala
            180                 185                 190

Ile Gly Phe Ser Val Ala Ile Gly His Leu Phe Ala Ile Asn Tyr Thr
        195                 200                 205

Gly Ala Ser Met Asn Pro Ala Arg Ser Phe Gly Pro Ala Val Ile Met
    210                 215                 220

Gly Asn Trp Glu Asn His Trp Ile Tyr Trp Val Gly Pro Ile Ile Gly
225                 230                 235                 240

Ala Val Leu Ala Gly Gly Leu Tyr Glu Tyr Val Phe Cys Pro Asp Val
                245                 250                 255

Glu Phe Lys Arg Arg Phe Lys Glu Ala Phe Ser Lys Ala Ala Gln Gln
            260                 265                 270

Thr Lys Gly Ser Tyr Met Glu Val Glu Asp Asn Arg Ser Gln Val Glu
        275                 280                 285

Thr Asp Asp Leu Ile Leu Lys Pro Gly Val Val His Val Ile Asp Val
    290                 295                 300

Asp Arg Gly Glu Glu Lys Lys Gly Lys Asp Gln Ser Gly Glu Val Leu
305                 310                 315                 320

Ser Ser Val Gly Gly Gly Gly Ser Val Glu Pro Lys Ser Ser Asp Lys
                325                 330                 335

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Arg Gly Pro
            340                 345                 350

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Tyr Ile Thr
        355                 360                 365

Arg Glu Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
    370                 375                 380

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
385                 390                 395                 400

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
                405                 410                 415

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
            420                 425                 430

Tyr Lys Cys Lys Val Ser Asn Lys Ala Arg Pro Ala Pro Ile Glu Lys
        435                 440                 445

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Thr Thr
    450                 455                 460

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
465                 470                 475                 480

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
                485                 490                 495

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Phe Pro Pro Val Leu
            500                 505                 510

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
        515                 520                 525

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
    530                 535                 540
```

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```
Ala Leu Lys Phe His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
545                 550                 555                 560

Lys


<210> SEQ ID NO 35
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: protein sequence - artificial

<400> SEQUENCE: 35

Gly Ser Ser Gly Gly Ser Gly Gly Gly Gly Ser
1               5                   10


<210> SEQ ID NO 36
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: protein sequence - artificial

<400> SEQUENCE: 36

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1               5                   10                  15


<210> SEQ ID NO 37
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: protein sequence - artificial

<400> SEQUENCE: 37

Ile Glu Gly Arg Met Asp
1               5


<210> SEQ ID NO 38
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: protein sequence - artificial

<400> SEQUENCE: 38

Gly Gly Gly Gly Ser
1               5
```

The invention claimed is:

1. A Seldeg comprising:

(A) a targeting component, having a protein or a protein fragment configured to specifically bind to a cell surface receptor or a cell surface molecule; wherein said protein or protein fragment is selected from the group consisting of:

(1) an antibody Fc fragment, which is

(i) engineered to have an increased binding affinity for FcRn at a pH greater than 6.8 and less than 7.5; and

(ii) has a reduced binding affinity for FcγRs and/or complement (C1q), compared with a wild-type Fc fragment;

(2) an antibody specific for a cell-surface ligand, wherein the Fc fragment of said antibody is

engineered to have a reduced binding affinity for FcγRs and/or complement (C1q), compared with a wild-type Fc fragment;

and

(3) a ligand for a cell-surface receptor, wherein said ligand is fused to an antibody Fc fragment which is

engineered to have a reduced binding affinity for FcγRs and/or complement (C1q), compared with a wild-type Fc fragment;

and

(B) a monovalent antigen component, having a single molecule of an antigen, antigen fragment or antigen mimetic configured to specifically bind a target antigen-specific antibody;

wherein the targeting component is fused directly or indirectly to the antigen component,

and

wherein said protein or protein fragment comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ

ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34; and a sequence having at least 95% identity thereto.

2. The Seldeg of claim **1**, comprising at least a first targeting component and a second targeting component, wherein the protein or protein fragment of the first targeting component is configured to bind to a different cell surface receptor or a different cell surface molecule than the protein or protein fragment of the second targeting component.

3. The Seldeg of claim **2**, wherein the targeting protein component comprises a heterodimer of two immunoglobulin Fc fragments in which one immunoglobulin Fc fragment of the heterodimer is fused to the antigen component and the other immunoglobulin Fc fragment is not.

4. The Seldeg of claim **1**, wherein the antigen component is fused to one immunoglobulin Fc fragment at an N-terminus or a C-terminus of a hinge-CH2-CH3 domain of the immunoglobulin Fc fragment.

5. The Seldeg of claim **1** wherein said protein or protein fragment comprises a combination selected from the group consisting of i) SEQ ID NO: 2 plus SEQ ID NO: 6, ii) SEQ ID NO: 4 plus SEQ ID NO: 6, iii) SEQ ID NO: 8 plus SEQ ID NO: 10, iv) SEQ ID NO: 12 plus SEQ ID NO: 14, v) SEQ ID NO: 20 plus SEQ ID NO: 22 plus SEQ ID NO: 24, vi) SEQ ID NO: 30 plus SEQ ID NO: 6, vii) SEQ ID NO: 32 plus SEQ ID NO: 6, viii) SEQ ID NO: 34 plus SEQ ID NO: 6, and a sequence having at least 95% identity thereto.

6. The Seldeg of claim **1** wherein:

the target antigen specific antibody is an anti-MOG antibody;

the targeting component comprises a heterodimer of

(i) residues **1-117** of MOG linked either directly or via a linker to an immunoglobulin Fc fragment; and

(ii) an immunoglobulin Fc fragment;

wherein the immunoglobulin Fc fragment is derived from IgG1 and comprises mutations of L234A, L235A, P329G (EU numbering system) to reduce FcγR and C1q binding and M252Y, S254T, T256E, H433K, N434F (EU numbering system) to increase FcRn binding;

and wherein component (i) of the heterodimer has at least 95% sequence identity to SEQ ID NO: 2 and component (ii) of the heterodimer has at least 95% sequence identity to SEQ ID NO: 6.

7. A method of depleting target antigen-specific antibody from a patient, the method comprising:

administering to the patient a Seldeg according to claim **1** in an amount sufficient to remove at least 50% of the target antigen-specific antibody from a circulation or a target tissue in the patient.

8. The method of claim **7**, comprising administering the Seldeg in an amount sufficient to remove at least 50% of the target antigen-specific antibody from the circulation or the target tissue in the patient within 24 hours of administration.

9. The method of claim **7**, comprising administering the Seldeg in an amount sufficient to remove at least 90% of the target antigen-specific antibody from the circulation or the target tissue in the patient within 48 hours of administration.

10. The method of claim **7**, comprising administering the Seldeg in an amount sufficient to remove at least 50% of the target antigen-specific antibody from the circulation or the target tissue in the patient within 48 hours of administration.

11. The method of claim **7**, wherein the Seldeg removes less than 10% of non-target antibodies in the circulation or in the tissue targeted by the target antigen-specific antibody.

12. The method of claim **7**, wherein the Seldeg removes an amount of non-targeted antibodies in the circulation or in the target tissue of the patient that does not cause a clinically adverse effect in the patient.

13. The method of claim **7**, wherein the Seldeg removes less than 1% of non-target antibodies in the circulation or in a tissue targeted by the target antigen-specific antibody.

14. The method of claim **7**, wherein the Seldeg causes degradation of the target antigen-specific antibody by a cell expressing the cell surface receptor or cell surface molecule.

15. The method of claim **7**, wherein the Seldeg is administered to a patient with an autoimmune disease and the target antigen-specific antibody specifically binds to an autoantigen.

16. The method of claim **7**, wherein the Seldeg is administered to a patient receiving a transplanted organ and the target antigen-specific antibody specifically binds to an antigen on the transplanted organ.

17. The method of claim **7**, wherein the Seldeg is administered to increase contrast during tumor imaging and the target antigen-specific antibody specifically binds to a tumor antigen.

18. The method of claim **7**, wherein the target-specific antibody has been administered to the patient.

19. The method of claim **7**, wherein the Seldeg is administered prior to the delivery of a therapeutic agent, if the patient has antibodies specific for the therapeutic agent, and the Seldeg is configured to target the antibodies specific for the therapeutic agent.

20. The method of claim **7**, wherein the Seldeg is administered to improve contrast in diagnostic imaging.

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