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(54) Title: ANTI-SURVIVIN ANTIBODIES FOR CANCER THERAPY

(57) Abstract: Provided are survivin specific antibodies, nucleic acids encoding the antibodies and methods for treating tumors comprising survivin-expressing cells by administration of the antibodies. The antibody compositions were found to be effective in inhibiting the growth of tumors.

ANTI-SURVIVIN ANTIBODIES FOR CANCER THERAPY

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional patent application no. 62/214,242, filed on September 4, 2015, the disclosure of which is incorporated herein by reference.

BACKGROUND OF THE DISCLOSURE

[0002] Survivin is an intracellular protein that belongs to a family of apoptosis inhibitors. Survivin acts in concert with the mitotic spindle apparatus to regulate cell division. It is expressed in certain cells during the G2/M phase of the cell cycle and associates with the spindle microtubule organizing center during this phase of cell cycle progression. Survivin functions in critical roles at a number of different cellular loci to regulate the cell cycle and to inhibit apoptotic cell death. It is frequently expressed by cancer cells of many different types, but uncommonly by normal adult tissues. Survivin peptide sequences have been used to develop vaccination strategies. While the survival of patients with some cancers has improved, challenges remain, particularly for those with advanced disease at diagnosis. As such, there continues to be a need to develop additional strategies to combat cancer.

SUMMARY OF THE DISCLOSURE

[0003] The present disclosure provides compositions and methods for treatment of tumors that comprise survivin-expressing cells. The disclosure provides isolated antibodies, including monoclonal and polyclonal antibodies and fragments and variants thereof, compositions comprising the antibodies, nucleic acid molecules encoding the antibodies or portions thereof or variants thereof, vectors comprising the nucleic acid molecules, cells comprising the antibodies and/or nuclei acid molecules, kits comprising one or more antibodies or nucleic acid molecules, and methods of using the antibodies or nucleic acid molecules or cells comprising the antibodies or nucleic acid molecules to inhibit the growth of tumors.

[0004] In one aspect, the disclosure provides an isolated antibody, which may be a polyclonal or a monoclonal antibody (mAb), which is specifically reactive against one or more epitopes of survivin. The antibody may be generated in response to administration of a peptide of survivin or a modification thereof. For example, an antibody can be generated in

response to a peptide, which may be 9 to 23 amino acids long and comprises the core sequence QMFFCF (SEQ ID NO:3).

[0005] An antibody of this disclosure can be a monoclonal antibody comprising a heavy chain variable region (VH) comprising a complementarity-determining region (CDR) 1 having a sequence set forth in SEQ ID NO:7, a CDR2 having a sequence set forth in SEQ ID NO:8 and a CDR3 having a sequence set forth in SEQ ID NO:9, and a light chain variable region (VL) comprising a CDR1 having a sequence set forth in SEQ ID NO:10, a CDR2 having a sequence set forth in SEQ ID NO:11 and a CDR3 having a sequence set forth in SEQ ID NO:12; or a monoclonal antibody comprising a VH comprising a CDR1 having a sequence set forth in SEQ ID NO:13, a CDR2 having a sequence set forth in SEQ ID NO:14 and a CDR3 having a sequence set forth in SEQ ID NO: 5, and a VL comprising a CDR1 having a sequence set forth in SEQ ID NO:16, a CDR2 having a sequence set forth in SEQ ID NO:17 and a CDR3 having a sequence set forth in SEQ ID NO:18.

[0006] The antibodies of the present disclosure may be chimeric, human, or humanized antibodies. In a chimeric or humanized antibodies, some portions of the heavy and/or light chains may be identical or homologous to sequences from one species while other portions may be identical or homologous to sequences from a different species. For example, murine monoclonal antibodies may be isolated or generated and then portions of these antibodies (or sequence information derived therefrom) used for generating chimeric or humanized antibodies. For example, mice may be immunized with one or more survivin peptides and then ascites fluid samples can be collected. The samples can be screened and selected to develop a panel of monoclonal antibodies and corresponding hybridoma cell lines. Portions or sequences from the monoclonal antibodies can then be used to generate chimeric or humanized antibodies. An antibody of the present disclosure can also be an antibody fragment, a single chain, a bispecific or multispecific antibody.

[0007] The disclosure provides nucleic acid molecules comprising sequences encoding portions or all of the antibodies (including mAbs) sequences. The disclosure also provides cells comprising the nucleic acid molecules.

[0008] This disclosure provides a method of treating a tumor in an individual in need of treatment comprising administering to the individual a composition comprising one or more antibodies that are specific for survivin, such as, for example, human survivin.

BRIEF DESCRIPTION OF THE FIGURES

[0009] Figure 1. Representation of effect of anti-survivin monoclonal antibody on an intracranial glioma model in C57BL/6 mice with GL261 glioma. Mice were administered anti-survivin antibody once every 7 days post tumor implantation. Percent survival is shown in as a function or time. IgG is normal mouse non-specific IgG. Control is untreated, tumor implanted mice.

[0010] Figure 2. Representation of effect of anti-survivin polyclonal and monoclonal antibodies on a subcutaneous tumor model in C57BL/6 mice with GL261 glioma. Mice were administered the indicated treatments once every 7 days post tumor implantation. SurVaxM is the survivin vaccine; anti-survivin sera (antibody) was derived from non-tumor bearing pooled mice receiving active survivin vaccine or survivin peptides. Control is untreated, tumor implanted mice.

[0011] Figure 3. Representation of effect of anti-survivin polyclonal antibodies on a subcutaneous tumor model in C57BL/6 mice with GL261 glioma. Mice were administered the indicated treatments once every 7 days post tumor implantation. SurVaxM is the survivin vaccine; anti-survivin sera (antibody) was derived from non-tumor bearing pooled mice receiving active SurVaxM vaccine. Mice were followed up to 50 days.

[0012] Figure 4. Representation of effect of two monoclonal antibodies against B16 murine melanoma in Nude (immunocompromised) mice. Tumor volume is shown for groups receiving non-specific IgG, mAb 2C2 and mAb H30. Each point represents one animal.

[0013] Figure 5. Representation of effect of two monoclonal antibodies against B16 murine melanoma in C57Bl/6 (immuno-competent) mice. Tumor volume is shown for groups receiving non-specific IgG, mAb 2C2 and mAb H30. Each point represents one animal.

[0014] Figure 6. Representation of effect of two monoclonal antibodies against B16 murine melanoma in Nude (immunocompromised) mice as a function of time. Tumor volume is shown for groups receiving non-specific IgG, mAb 2C2 and mAb H30.

[0015] Figure 7. Representation of effect of two monoclonal antibodies against B16 murine melanoma in C57Bl/6 (immuno-competent) mice as a function of time. Tumor volume is shown for groups receiving non-specific IgG, mAb 2C2 and mAb H30.

[0016] Figure 8. Representation of effect of two monoclonal antibodies against GL261 murine glioma in Nude (immunocompromised) mice. Tumor volume is shown for control (untreated), groups receiving non-specific IgG, mAb 2C2 and mAb H30. Each point represents one animal.

[0017] Figure 9. Representation of effect of two monoclonal antibodies against GL261 murine glioma in C57Bl/6 (immuno-competent) mice. Tumor volume is shown for groups receiving control, non-specific IgG, mAb 2C2 and mAb H30. Each point represents one animal.

[0018] Figure 10. Representation of effect of two monoclonal antibodies against GL261 murine glioma in C57Bl/6 (immuno-competent) mice as a function of time. Tumor volume is shown for groups receiving control, non-specific IgG, mAb 2C2 and mAb H30.

[0019] Figure 11. Representation of effect of two monoclonal antibodies against GL261 murine glioma in Nude (immunocompromised) mice as a function of time. Tumor volume is shown for groups receiving control, non-specific IgG, mAb 2C2 and mAb H30.

[0020] Figure 12. Representation of generation of total IgG in patients who were administered a survivin vaccine (SEQ ID NO:4). Data is shown for 8 patients. Serum ELISA studies show progressive increase in serum IgG reactivity to wild type survivin peptide (amino acids 53-67 (SEQ ID NO:27).

[0021] Figure 13. Representation of generation of survivin specific IgG in patients who were administered a survivin vaccine (SEQ ID NO:4). Data is shown for 8 patients. Serum ELISA studies show progressive increase in serum IgG reactivity to modified survivin peptide (amino acids 53-67/M57 – SEQ ID NO:4).

DETAILED DESCRIPTION OF THE DISCLOSURE

[0022] The present disclosure is based on our observations that antisera from survivin peptide-vaccinated mice and purified murine monoclonal antibodies against survivin significantly inhibit tumor growth in animal models. This is surprising because survivin is an intracellular protein that is thought not to be secreted by cells or displayed on the cell surface, except within the context of MHC class I presentation. As such, antibody-mediated (passive) survivin immunotherapy would not be expected to be effective. However, we have found that it is.

[0023] This disclosure provides isolated antibodies and fragments thereof, isolated nucleic acid molecules encoding antibodies or fragments thereof, cells producing antibodies or fragments thereof, vectors or cells comprising nucleic acids encoding antibodies or fragments thereof, compositions comprising any of the foregoing, methods of making any of the foregoing, and methods of using the antibodies and fragments thereof, or nucleic acid molecules in the treatment of cancers such as those involving survivin-expressing tumors.

[0024] A description of the sequence listings with this application is as follows:

[0025] SEQ ID NO:1 is an amino acid sequence representing a 23 amino acid long fragment of human survivin.

[0026] SEQ ID NO:2 is a variant of SEQ ID NO:1 with a single amino acid change

[0027] SEQ ID NO:3 is a six amino acid long fragment of SEQ ID NO:2.

[0028] SEQ ID NO:4 is a fifteen amino acid long fragment of SEQ ID NO:2 and comprises the sequence of SEQ ID NO:3.

[0029] SEQ ID NO:5 is a ten amino acid long fragment of SEQ ID NO:2 and comprises the sequence of SEQ ID NO:3.

[0030] SEQ ID NO:6 is a nine amino acid long fragment of SEQ ID NO:2 and comprises the sequence of SEQ ID NO: 3.

[0031] SEQ ID NO:7 is an amino acid sequence for VH CDR1 for mAb 2C2E7

[0032] SEQ ID NO:8 is an amino acid sequence for VH CDR2 for mAb 2C2E7

[0033] SEQ ID NO:9 is an amino acid sequence for VH CDR3 for mAb 2C2E7

[0034] SEQ ID NO:10 is an amino acid sequence for VL CDR1 for mAb 2C2E7

[0035] SEQ ID NO:11 is an amino acid sequence for VL CDR2 for mAb 2C2E7

[0036] SEQ ID NO:12 is an amino acid sequence for VL CDR3 for mAb 2C2E7

[0037] SEQ ID NO:13 is an amino acid sequence for VH CDR1 for mAb 30H3D2

[0038] SEQ ID NO:14 is an amino acid sequence for VH CDR2 for mAb 30H3D2

[0039] SEQ ID NO:15 is an amino acid sequence for VH CDR3 for mAb 30H3D2

[0040] SEQ ID NO:16 is an amino acid sequence for VL CDR1 for mAb 30H3D2

[0041] SEQ ID NO:17 is an amino acid sequence for VL CDR2 for mAb 30H3D2

[0042] SEQ ID NO:18 is an amino acid sequence for VL CDR3 for mAb 30H3D2

[0043] SEQ ID NO:19 is an amino acid sequence for heavy chain variable region from mAb 2C2E7.

[0044] SEQ ID NO:20 is an amino acid sequence for light chain variable region from mAb 2C2E7.

[0045] SEQ ID NO:21 is an amino acid sequence for heavy chain variable region from mAb 30H3D2.

[0046] SEQ ID NO:22 is an amino acid sequence for light chain variable region from mAb 30H3D2.

[0047] SEQ ID NO:23 is a nucleotide sequence encoding the heavy chain variable region of 2C2E7 (it encodes the amino acid sequence of SEQ ID NO:19).

[0048] SEQ ID NO:24 is a nucleotide sequence encoding the light chain variable region of 2C2E7 (it encodes the amino acid sequence of SEQ ID NO:20).

[0049] SEQ ID NO:25 is a nucleotide sequence encoding the heavy chain variable region of 30H3D2 (it encodes the amino acid sequence of SEQ ID NO:21).

[0050] SEQ ID NO:26 is a nucleotide sequence encoding the light chain variable region of 30H3D2 (it encodes the amino acid sequence of SEQ ID NO:22).

[0051] SEQ ID NO:27 is a fifteen amino acid long fragment of human survivin.

[0052] While vaccines provide one way forward in anti-survivin cancer immunotherapy, there are several advantages of using a passive immunotherapy with antibodies. For example, a humanized monoclonal antibody: 1) would not be HLA-restricted (unlike peptide vaccines), 2) could potentially have immediate action against cancer cells in patients who are severely immunocompromised by their tumors, 3) would be doseable, and 4) could be used in conjunction with a vaccine or other drugs or therapies such as, for example, radiation therapy, to exploit alternative or complementary mechanisms of action. One or more the above advantages are also applicable to mAbs in general, including chimeric, human and humanized antibodies.

[0053] The term "survivin peptide" or "survivin peptides" as used herein means fragments of full length survivin and includes variants of the peptides which can generate antibodies that react with the wild type survivin, such as human survivin. The term "anti-survivin antibodies" as used herein means antibodies that are generated in response to survivin or one or more survivin peptides (including variants thereof).

[0054] In one aspect, this disclosure provides compositions comprising antibodies or fragments thereof, including human antibodies, humanized antibodies, or chimeric antibodies, which are reactive against one or more epitopes of survivin. Examples of suitable survivin epitopes or variants thereof are provided in U.S. Patent Nos. 7,943,138, and 8,580,269, the disclosures of which are incorporated herein by reference. The compositions of the present disclosure comprise antibodies generated in response to administering a peptide that is identical to a sequence within human survivin or is a variant thereof (such as at least 95% identical). For example, antibodies may be generated in and isolated from an individual following administration of a peptide that is variant of the following portion of survivin sequence ENEPDLAQCFFCFKELEGWEPDD (SEQ ID NO:1). The variant can be ENEPDLAQMFFCFKELEGWEPDD (SEQ ID NO:2 - a C to M change at position 9 of SEQ ID NO:1). The peptides administered can be from 9 to 23 (including all integers therebetween) contiguous amino acids of SEQ ID NO:2, wherein the peptide comprises the core sequence of QMFFCF (SEQ ID NO:3). Exemplary survivin peptides include DLAQMFFCFKELEGW (SEQ ID NO:4), AQMFFCFKEL (SEQ ID NO:5), and

QMFFCFKEL (SEQ ID NO:6). The isolated antibodies or fragments thereof may be used without modifications, or they may be engineered, such as, for example, to generate chimeric or humanized antibodies or various fragments as described therein. In one embodiment, humanized antibodies or fragments thereof are generated that are reactive against the peptide DLAQMFFCFKELEGW (SEQ ID NO:4).

[0055] The term "Antibody" as used herein can encompass whole antibody molecules, full-length immunoglobulin molecules, such as naturally occurring full-length immunoglobulin molecules or full-length immunoglobulin molecules formed by immunoglobulin gene fragment recombinatorial processes, as well as antibody fragments. Antibody fragments can be fragments comprising at least one antibody-antigen binding site. Antibody fragments can, for example, exhibit specific binding to survivin or fragments thereof comprising the motif DLAQCFFCFKELEGW (SEQ ID NO:27). The term "antibody" can include e.g. monoclonal, polyclonal, multispecific (for example bispecific), recombinant, human, chimeric and humanized antibodies. The term "antibody" can also encompass recombinantly expressed antigen binding proteins and antigen binding synthetic peptides. Further, the term "antibody" can encompass minibodies, and diabodies, all of which preferably exhibit specific binding to survivin of a fragment thereof, especially human survivin. The term "antibody", as used herein, can also encompass immunoglobulins produced in vivo, as well as those produced in vitro, such as, for example, by a hybridoma. An antibody of the present disclosure may be modified by, for example, acetylation, formylation, amidation, phosphorylation, or polyethylene glycolation (PEGylation), as well as glycosylation. The term "an antibody" as used herein is intended to cover all antibodies disclosed herein. For example, the term "an antibody" can refer to monoclonal, polyclonal, chimeric, human, or humanized antibodies, or antigen (i.e., survivin) binding fragments thereof.

[0056] Administration of survivin peptides can be used for generation of polyclonal antibodies. For example, suitable animals can be administered one or more survivin peptides and serum can be collected. Further, human anti-survivin antibody-expressing cells can be isolated from immunized animals or patients vaccinated with survivin or survivin peptides – for example, from individuals who may be participating in clinical trials. IgG+ memory B cells from patient samples can be expanded and induced to differentiate into IgG-secreting cells, which can be screened for high-affinity target (survivin peptide) binding. The cells can also be used for generation of hybridomas. Variable regions of antibody genes can be cloned from isolated cells by RT-PCR using the PIPE method (Dodev TS et al. (2014) Scientific

Reports 4, 5885. doi:10.1038/srep058853). Recombinant human, humanized or chimeric mAbs can be constructed from these molecules and can be expressed and screened in functional and binding affinity assays and for anti-tumor activity. In this regard, we have been able to detect specific antibodies by ELISA in several patients in a clinical study. Samples can be frozen for later use for isolation of memory B cells.

[0057] The antibodies of the disclosure may be whole immunoglobulin molecules such as polyclonal or monoclonal antibodies or may be antigen-binding fragments thereof, including but not limited to, Fab, F(ab'), F(ab')2, Fv, dAb, Fd, CDR fragments, single-chain antibodies (scFv), bivalent single-chain antibodies, single-chain phage antibodies, diabodies, nanobodies and the like. The fragments of the antibodies may be produced synthetically or by enzymatic or chemical cleavage of intact immunoglobulins or may be genetically engineered by recombinant DNA techniques. These techniques are well known in the art.

[0058] In one embodiment, this disclosure provides isolated antibodies. By the term "isolated" it is meant that the antibody or the fragment thereof, is separated and/or recovered from its natural environment. The isolation of the antibody from its natural environment can be such that the antibody can be used without interference from other active agents (such as other proteins) that normally are present in its natural environment.

[0059] In one embodiment, this disclosure provides generating and isolating single domain antibodies or nanobodies produced by camelids in response to introducing survivin or survivin peptides into the camelids. The nanobodies are typically heavy chain antibodies and thus contain heavy chain homodimers and do not contain antibody light chains. These antibodies typically comprise a single variable domain and two constant domains (CH2 and CH3).

[0060] The antibodies of the present disclosure may be obtained from a human or a non-human animal. In many mammals, intact immunoglobulins have two heavy chains and two light chains. Each of the light chains is covalently linked to a heavy chain by a disulfide bond. The two heavy chains are linked to each other by additional disulfide bonds. The light chain typically has one variable domain (VL) and one constant domain (CL). The heavy chain can also have one variable domain (VH). The variable domains contain complementarity-determining regions (CDRs). The heavy chain can further have three or four constant domains (CHI, CH2, CH3 and CH4). The variability of the constant domains results is various isotypes such as IgA, IgD, IgE, IgG, and IgM.

[0061] The CDRs are primarily responsible for binding to an epitope of an antigen. The CDRs of each chain are typically referred to as CDR1, CDR2, and CDR3, numbered

sequentially starting from the N-terminus, and are typically identified by the chain in which the particular CDR is located. Thus, a V_H CDR3 (or VH-CDR3) is located in the variable domain of the heavy chain of the antibody in which it is found, whereas a V_L CDR1 (or VL-CDR1) is the CDR1 from the variable domain of the light chain of the antibody in which it is found. An antibody that binds survivin or survivin peptides, for example, will have a specific V_H region and the V_L region sequence, and thus specific CDR sequences. Antibodies with different specificities (i.e. different combining sites for different antigens) have different CDRs.

[0062] The terms V_H or VH as used herein refer to the variable region of an immunoglobulin heavy chain, including a heavy chain of an Fv, scFv, dsFv or Fab, and the terms V_L or VL refer to the variable region of an immunoglobulin light chain, including a light chain of an Fv, scFv, dsFv or Fab.

[0063] The term "monoclonal antibody" refers to an antibody produced by a single clone of B-lymphocytes or by a cell into which the light and/or heavy chain genes of a single antibody have been transfected. Monoclonal antibodies are produced by methods known to those of skill in the art, for instance by making hybrid antibody-forming cells from a fusion of myeloma cells with immune spleen cells. For example, mice (or other suitable animals) may be immunized with one or more survivin peptides and then ascites fluid samples can be collected. The samples can be screened and selected to develop a panel of monoclonal antibodies and corresponding hybridoma cell lines. Murine (or other) monoclonal antibodies may be isolated or generated and then humanized, if desired.

[0064] An antibody of the present disclosure can be an antibody of any class. For example, an antibody of the present invention can be an antibody isotype IgG1, IgG2, IgG3, IgG4, IgM, IgA, IgD or IgE. For example, the antibody can be IgG2b. The term "isotype", as used herein, can in particular refer to the antibody class (such as e.g. IgG) that is encoded by heavy chain constant region genes. Sequences of human immunoglobulin constant regions are known in the art and are available in public databases such as National Center for Biotechnology Information (NCBI), U.S. National Library of Medicine.

[0065] The term "chimeric antibody" refers to an antibody which has framework residues from one species, such as human, and CDRs (which generally confer antigen binding) from another species, such as a murine antibody that specifically binds survivin. In a chimeric antibody, some portions of the heavy and/or light chains may be identical or homologous to sequences from a particular species while other portions may be identical or homologous to sequences from a different species. Chimeric antibodies generally exhibit

decreased immunogenicity and increased stability. Techniques for cloning murine immunoglobulin variable domains known in the art – such as, for example, see Orlandi et al., Proc. Natl Acad. Sci. USA 86: 3833 (1989), and Leung et al., Hybridoma 13:469 (1994). As an example of a chimeric antibody, polynucleotides encoding the variable domains of the light chain or the heavy chain of an antibody derived from an animal (e.g., mouse, rat, or chicken) other than human can be linked to polynucleotides encoding the constant domains of the light chain or the heavy chain derived from a human antibody to produce a polynucleotide (such as DNA) encoding a chimeric antibody. Examples of chimeric antibodies include those comprising SEQ ID NOs:19 and 20, and those comprising SEQ ID NOs:20 and 21.

[0066] A "human" antibody (also called a "fully human" antibody) is an antibody that includes human framework regions and all of the CDRs from a single or different human immunoglobulins. Thus, frameworks from one human antibody can be engineered to include CDRs from a different human antibody. Methods for producing human antibodies are known in the art – such as, for example, see Mancini et al., 2004, New Microbiol. 27:315-28; Conrad and Scheller, 2005, Comb. Chem. High Throughput Screen. 8:117-26.

[0067] A "humanized antibody" is typically a human antibody that has one or more amino acid residues imported into it (i.e., introduced into it) from a source that is non-human. For example, a humanized antibody is a recombinant protein in which the CDRs of an antibody from a species such as rodent, rabbit, dog, goat, or horse are imported into human heavy and light variable domains. The constant domains (also referred to as framework regions) of the antibody molecule are generally the same as those of a human antibody. The non-human immunoglobulin providing the CDRs can be termed as "donor" and the human immunoglobulin providing the framework can be termed as "acceptor". For example, all the CDRs can be from the donor immunoglobulin in a humanized immunoglobulin. Constant regions need not be always present, but if they are, they can be substantially identical to human immunoglobulin constant regions, i.e., at least about 85-90%, such as about 95% or more identical. A humanized antibody binds to the same antigen as the donor antibody that provides the CDRs. The acceptor framework of a humanized immunoglobulin or antibody may have a limited number of substitutions by amino acids taken from the donor framework. Humanized or other monoclonal antibodies can have additional conservative amino acid substitutions which have substantially no effect on antigen binding or other immunoglobulin functions. Humanized immunoglobulins can be constructed by means of genetic engineering (see for example, U.S. Pat. No. 5,585,089, and U.S. Publication No. 2010/0196266). For example, murine monoclonal antibodies may be isolated or generated and then humanized.

Examples of humanized antibodies include those comprising CDRs having sequences of SEQ ID NOs:7 through 12, and those comprising CDRs having sequences of SEQ ID NOs:13 through 18.

[0068] Antibody fragments can be produced by enzymatic digestion. For example, papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a "Fc" fragment. The Fab fragment contains an entire L chain and the variable region domain of the H chain (VH), and the first constant domain of one heavy chain. Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment that roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is capable of cross-linking antigen. "Fv" is the minimum antibody fragment that contains a complete antigen-recognition and -binding site and single-chain Fv also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the VH and VL antibody domains connected into a single polypeptide chain. The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments with short linkers between the VH and VL domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. A single domain antibody (sdAb) is an antibody fragment which has a single monomeric variable antibody domain. ScAbs can be made from heavy-chain antibodies found in camelids. An antibody fragment can be a single variable region or a peptide consisting of or comprising a single CDR. A single-chain antibody has a heavy chain variable domain and a light chain variable domain linearly linked to each other via a linker. A polynucleotide (such as DNA) encoding the single-chain antibody can be produced by binding a polynucleotide encoding the heavy chain variable domain, a polynucleotide encoding the linker (typically 10-20 nucleotides), and a polynucleotide encoding the light chain variable domain, with the heavy chain variable domain and the light chain variable domain being both derived from a human antibody.

[0069] The antibodies of the present invention can be bispecific or multispecific. Bispecific antibodies (diabodies) are antibodies that have binding specificities for at least two different epitopes of an antigen, such as two different epitopes of survivin. For example, a polynucleotide (such as DNA) encoding a bispecific antibody can be produced by, for example, linking in order a polynucleotide encoding a heavy chain variable region A, a polynucleotide encoding a light chain variable region B, a polynucleotide encoding a heavy chain variable domain B, and a polynucleotide encoding a light chain variable domain A.

Preferably, the heavy chain variable domain and the light chain variable domain are both derived from a human antibody.

[0070] The present disclosure provides variants of sequences set forth in SEQ ID NOs: 1 through 29. For example, variants can have at least 90%, at least 95%, at least 98% or at least 99% sequence identity to the sequences disclosed in SEQ ID NOs:1-27.

[0071] The present disclosure provides T cells transduced to express a chimeric antigen receptor (CAR). CAR molecules of the present disclosure combine antibody-based specificity for survivin with a T cell receptor-activating intracellular domain to generate a chimeric protein that exhibits specific anti-survivin, and therefore, anti-tumor cellular immune activity. A CAR molecule can comprise one or more CDRs of the heavy or light variable regions. This disclosure further provides T cells genetically modified to stably express the CAR. T cells expressing a CAR are referred to herein as CAR T cells or CAR modified T cells. For example, T cells can be genetically modified to stably express the CAR that combines a survivin recognition domain of a specific antibody, such as a monoclonal antibody described herein, with an intracellular domain of the CD3-zeta chain into a single chimeric protein.

[0072] As an example, this disclosure provides monoclonal antibodies, which can be isolated monoclonal antibodies, which specifically bind to survivin, which can be human survivin. As an example, a mAb designated 2C2 and a mAb designated H30 (or 30H3) are provided. A subclone of mAb 2C2 used for final antibody sequencing and IgG purification was designated 2C2E7, and a subclone of mAb H30 used for final antibody sequencing and IgG purification was designated 30H3D2. An antibody comprises a heavy chain variable region and a light chain variable region. The heavy chain variable region comprises a VH CDR1, a VH CDR 2, and a VH CDR3, and the light chain variable region comprises a VL CDR1, a VL CDR2, and a VL CDR3. As an example, the VH CDR1 has an amino acid sequence TYGMS (SEQ ID NO:7), the VH CDR2 has an amino acid sequence WINPYSGVPTYAVDFKG (SEQ ID NO:8), and the VH CDR3 has an amino acid sequence GGRRGDFGY (SEQ ID NO:9); and the VL CDR1 has an amino acid sequence SASSSISYMH (SEQ ID NO:10), the VL CDR2 has an amino acid sequence DTSKLAS (SEQ ID NO:11), and the VL CDR3 has an amino acid sequence HQRSSHHT (SEQ ID NO:12). As another example, the VH CDR1 has an amino acid sequence SYGMS (SEQ ID NO:13), the VH CDR2 has an amino acid sequence TISSGGSHTYYPDSVRG (SEQ ID NO:14), and the VH CDR3 has an amino acid sequence HPIYYYISSYAMDY (SEQ ID NO:15); and the VL CDR1 has an amino acid sequence RSSQSLVHSTGNTYLH (SEQ ID

NO:16), the VL CDR2 has an amino acid sequence KVSNRFS (SEQ ID NO:17), and the VL CDR3 has an amino acid sequence SQSTHVPPT (SEQ ID NO:18).

[0073] An antibody of the present disclosure can be an antibody which has VH CDRs that have 1 or 2 amino acids that are different than the sequence set forth in SEQ ID Nos:7, 8, 9, and/or which has VL CDRs that have 1 or 2 amino acids that are different than the sequence set forth in SEQ ID NOs:10, 11, 12. An antibody of the present disclosure can be an antibody which has VH CDRs that have 1 or 2 amino acids that are different than the sequence set forth in SEQ ID Nos:13, 14, 15, and/or which has VL CDRs that have 1 or 2 amino acids that are different than the sequence set forth in SEQ ID NOs:16, 17, 18.

[0074] An antibody of the present disclosure can be an antibody wherein the heavy chain variable region comprises the sequence of SEQ ID NO: 19, and the light chain variable region comprises the sequence of SEQ ID NO: 20. In the sequence of SEQ ID NO:19, amino acids 1 through 19 represent a leader sequence, amino acids 20 through 49 represent framework region (FR) 1, amino acids 50 through 54 represent CDR1, amino acids 55 through 68 represent FR2, amino acids 69 through 85 represent CDR2, amino acids 86 through 117 represent FR3, amino acids 118 through 126 represent CDR3, and amino acids 127 through 137 represent FR4. In the sequence of SEQ ID NO: 20, amino acids 1 through 22 represent a leader sequence, amino acids 23 through 45 represent FR1, amino acids 46 through 55 represent CDR1, amino acids 56 through 70 represent FR2, amino acids 71 through 77 represent CDR2, amino acids 78 through 109 represent FR3, amino acids 110 through 117 represent CDR3, and amino acids 118 through 127 represent FR4.

[0075] An antibody of the present disclosure can be an antibody comprising a heavy chain variable region comprising the sequence of SEQ ID NO:21, and a light chain variable region comprising the sequence of SEQ ID NO:22. In the sequence of SEQ ID NO:21, amino acids 1 through 19 represent a leader sequence, amino acids 20 through 49 represent FR1, amino acids 50 through 54 represent CDR1, amino acids 55 through 68 represent FR2, amino acids 69 through 85 represent CDR2, amino acids 86 through 117 represent FR3, amino acids 118 through 131 represent CDR3, and amino acids 132 through 142 represent FR4. In the sequence of SEQ ID NO: 22, amino acids 1 through 19 represent a leader sequence, amino acids 20 through 42 represent FR1, amino acids 43 through 58 represent CDR1, amino acids 59 through 73 represent FR2, amino acids 74 through 80 represent CDR2, amino acids 81 through 112 represent FR3, amino acids 113 through 121 represent CDR3, and amino acids 122 through 131 represent FR4.

[0076] An antibody of the present disclosure can be an antibody comprising a heavy chain variable region comprising a sequence of SEQ ID NO:19 and a light chain variable region comprising a sequence of SEQ ID NO:20, or variants thereof that have 90% to 99% sequence identity. An antibody of the present disclosure can be an antibody comprising a heavy chain variable region comprising a sequence of SEQ ID NO:21 and a light chain variable region comprising a sequence of SEQ ID NO:22, or variants thereof that have 90% to 99% sequence identity. An antibody can be an antibody comprising a heavy chain variable region comprising a sequence of SEQ ID NO:19 excluding the leader sequence (i.e., excluding amino acids 1 through 19) and/or a light chain variable region comprising a sequence of SEQ ID NO:20 excluding the leader sequence (i.e., excluding amino acids 1 through 22), or variants thereof that have 90% to 99% sequence identity. An antibody of the present disclosure can be an antibody comprising a heavy chain variable region comprising a sequence of SEQ ID NO:21 excluding the leader sequence (i.e., excluding amino acids 1 through 19) and/or a light chain variable region comprising a sequence of SEQ ID NO:22 excluding the leader sequence (i.e., excluding amino acids 1 through 19), or variants thereof that have 90% to 99% sequence identity.

[0077] An antibody of the present disclosure can be an antibody comprising a heavy chain variable region which has a sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:19 and which comprises a CDR1 having a sequence of SEQ ID NO:7, a CDR2 having a sequence of SEQ ID NO:8, and a CDR3 having a sequence of SEQ ID NO:9, and/or a light chain variable region which as a sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:20 and which comprises a CDR1 having a sequence of SEQ ID NO:10, a CDR2 having a sequence of SEQ ID NO:11, and a CDR3 having a sequence of SEQ ID NO:12.

[0078] An antibody of the present disclosure can be an antibody comprising a heavy chain variable region which has a sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:21 and which comprises a CDR1 having a sequence of SEQ ID NO:13, a CDR2 having a sequence of SEQ ID NO:14, and a CDR3 having a sequence of SEQ ID NO:15, and/or a light chain variable region which as a sequence which is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO:20 and which comprises a CDR1 having a sequence of SEQ ID NO:16, a CDR2 having a sequence of SEQ ID NO:17, and a CDR3 having a sequence of SEQ ID NO:18.

[0079] An antibody of the present disclosure can be a chimeric, human or humanized antibody comprising a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the sequences of SEQ ID NOs: 7, 8 and 9 respectively, and a light chain variable region comprising CDR1, CDR2, and CDR3 having the sequences of SEQ ID NOs: 10, 11 and 12 respectively, or comprising a heavy chain variable region comprising CDR1, CDR2 and CDR3 having the sequences of SEQ ID NOs: 13, 14 and 15 respectively, and a light chain variable region comprising CDR1, CDR2, and CDR3 having the sequences of SEQ ID NOs: 16, 17 and 18 respectively.

[0080] The present disclosure also provides isolated nucleotide sequences encoding all or portions of heavy chain variable regions for survivin specific antibodies. For example, the present disclosure provides an isolated nucleic acid molecule comprising the sequence of SEQ ID NOs: 23 or 25. An isolated nucleotide molecule of the present disclosure can encode all or portions of light chain variable regions for survivin specific antibodies. For example, the isolated nucleic acid molecule can comprise the sequence of SEQ ID NOs: 24 or 26. Variants of nucleic acid molecules can have at least 90% to at least 99% identity with the sequences of SEQ ID NOs: 23 or 25 for the heavy chain variable region or SEQ ID NOs: 24 or 26 for the light chain variable region.

[0081] The present disclosure also provides isolated nucleic acid molecules comprising or consisting of the sequence encoding one or more CDRs that recognize a survivin epitope – such as for example, sequences encoding SEQ ID NOs: 7 to 18. A nucleic acid molecule can consist of any of the sequences of SEQ ID NOs: 7 to 18, or a nucleic acid molecule can comprise one or more sequences of SEQ ID NOs: 7 to 18 and further comprise additional 1 to 50 nucleotides – generally flanking the sequences.

[0082] The disclosure provides cells comprising an expression vector or other polynucleotide sequence encoding the antibodies provided herein (including mAbs) or survivin binding fragments thereof. Nucleotide sequences encoding the mAbs or survivin binding fragments thereof can be expressed using any suitable expression vector, many of which are known in the art and/or are commercially available. A vector generally includes nucleic acid sequences, such as origin or replication that enables it to replicate in a host cell. A vector can also include selectable marker genes. Heavy and light chains can be expressed on a single expression vector, such as a plasmid or the heavy and light chains can be expressed on distinct plasmids in the same cell, after which the expressed heavy and light chains can form the conventional mAb architecture. The mAbs or survivin binding fragments

thereof can be isolated and/or purified using conventional techniques, given the benefit of the present disclosure.

[0083] The isolated monoclonal antibodies or fragments thereof can be labeled, such as with enzymatic, fluorescent or radioactive tags or can be conjugated to effector molecules such as, for example, toxins.

[0084] The present disclosure provides pharmaceutical compositions comprising the antibodies or fragments thereof, and pharmaceutically suitable carrier. Suitable carriers include excipients, or stabilizers which are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as acetate, Tris, phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; tonicifiers such as trehalose and sodium chloride; sugars such as sucrose, mannitol, trehalose or sorbitol; surfactant such as polysorbate; salt-forming counter-ions such as sodium; and/or non-ionic surfactants such as Tween or polyethylene glycol (PEG). The pharmaceutical compositions may comprise other therapeutic agents.

[0085] Compositions of the present disclosure can comprise one type of monoclonal antibody or more than one type of monoclonal antibody. A composition of the disclosure can have one or more of an antibody or fragment or variant thereof. A composition can have a monoclonal and a polyclonal antibody. A composition can comprise one or more subtypes of antibodies. For example, a composition can comprise a mixture of IgG or IgM or a mixture of one or more of IgG1, IgG2, and IgG2b. A composition of the present disclosure can comprise an antibody as the only active ingredient, wherein the antibody may be monoclonal, polyclonal, chimeric, human, humanized or combinations thereof. By “active ingredient” is meant that the ingredient has an anti-tumor effect by inhibiting tumor growth.

[0086] A pharmaceutical composition of the disclosure can comprise one or more antibodies at a concentration range from 0.1 mg/ml to 100 mg/ml, 1 mg/ml to 10 mg/ml, 1 mg/ml to 50 mg/ml, 1 mg/ml to 100 mg/ml, 10 mg/ml to 100 mg/ml, or 50 mg/ml to 100 mg/ml of each of the antibodies or total antibodies. For example, a pharmaceutical composition of the disclosure can comprise at least or about 0.1 mg/ml, at least or about 1

mg/ml, at least or about 5 mg/ml, at least or about 10 mg/ml, at least or about 50 mg/ml, at least or about 100 mg/ml of an antibody.

[0087] The compositions of the present disclosure may be administered by routine methods known in the art. For example, the compositions comprising antibodies or fragments thereof may be administered via intravenous, intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes, or by intracerebral or intra-spinal convection enhanced delivery or direct intratumoral injection. The antibodies may be administered parenterally directly at the target site (such as at or within a tumor). The compositions may be introduced as a single administration or as multiple administrations and may be introduced in a continuous manner over a period of time. In one embodiment, the composition may be administered daily for a period of at least 2 days such as, for example, for a period of 2-30 days (and all periods therebetween). In one embodiment, it is administered daily for 7-10 days. It may alternatively be administered at desired intervals (such as every 2, 3, 4, 5 days and the like).

[0088] It will be recognized by those of skill in the art that the form and character of the particular dosing regimen employed in the method of the invention will be dictated by the route of administration and other well-known variables, such as the size of the individual and the stage of the disease. Further, the compositions can be provided in the form of unit dosage forms for administration to an individual in need of treatment. Antibodies can be provided in a lyophilized form to be reconstituted prior to administration. The reconstitution medium can be sterile 0.9% saline solution or a suitable physiological buffer or water, or any other solution known in the art for reconstituting proteins prior to administration.

[0089] The disclosure also provides kits which can be used for administration to individuals in need of treatment. A kit, for example, can comprise one or more antibodies, which may be in a lyophilized form, optionally reconstitution media, and instructions for administration. A kit can comprise a single dose or multiple doses.

[0090] The disclosure provides a method for treating tumors, such as tumors that comprise survivin-expressing cells. Such tumors may be referred to herein as "survivin-expressing tumors". The term "treatment" refers to reduction in one or more symptoms or features associated with the presence of the particular condition being treated. Treatment does not necessarily mean complete remission, nor does it preclude recurrence or relapses. For example, the present disclosure provides a method for reducing the size of a tumor or arresting the growth of a tumor or reducing the rate of growth of a tumor (such as a tumor comprising survivin-expressing cells) or reducing any other symptom that is associated with

an individual being afflicted with the tumor – all of which are considered as "treatment" – comprising administering to an individual in need of treatment, a therapeutically effective amount of a composition comprising antibodies, or fragments thereof as described herein. In one embodiment, the method is a method of passive immunization.

[0091] Examples of tumors that can be treated by the present compositions include, but are not limited to, glioma, glioblastoma, medulloblastoma, multiple myeloma, melanoma, meningioma, breast adenocarcinoma, ovarian carcinoma, prostate carcinoma, leukemia, lymphoma, colon carcinoma, pancreatic cancer, hepatic cancer, kidney cancer, sarcoma and the like.

[0092] The method of the invention can be performed in conjunction with use of survivin peptides as a vaccine. The compositions of the invention can be administered prior to, concurrently, or subsequent to other therapies.

[0093] In one aspect, the present disclosure provides compositions comprising an isolated antibody which is reactive against one or more epitopes of survivin wherein the isolated antibody or the antigen-binding fragment thereof binds to one or more epitopes of survivin. The antibody may be generated in response to administration of a peptide having the sequence ENEPDLAQMFFCFKELEGWEPDD (SEQ ID NO:2) , or a fragment thereof (such as SEQ ID NO:4), wherein the fragment has from 9 to 23 (including all integers therebetween) contiguous amino acids of SEQ ID NO:2, and wherein the peptide comprises the core sequence of QMFFCF (SEQ ID NO:3). The composition may be such that the only antibody or antibodies present is/are the isolated antibody/antibodies generated in response to administration of survivin peptides. The composition may have other protein such as carrier proteins. The antibody may be a chimeric, human or a humanized antibody. The antibody may be a monoclonal or a polyclonal antibody, or a single chain, or multispecific antibody.

[0094] Reactivity of antibodies toward specific antigens can be measured by routine methods such as, for example, ELISA. Reactivity is an indication of the binding affinity. Binding affinity can also be measured by antigen/antibody dissociation rates or competition radioimmunoassays and the like. Specific binding of an antibody to an antigen means it binds the antigen with high affinity and does not specifically bind to unrelated antigens.

[0095] In one aspect, the disclosure provides a method of passive immunization comprising administering to an individual in need of treatment, a therapeutically effective amount of the composition comprising one or more antibodies generated in response to administration of a peptide having the sequence ENEPDLAQMFFCFKELEGWEPDD (SEQ ID NO:2) , or a fragment thereof (such as SEQ ID NO:4), wherein the fragment has from 9 to

23 (including all integers therebetween) contiguous amino acids of SEQ ID NO:2, and wherein the peptide comprises the core sequence of QMFFCF (SEQ ID NO:3), and which antibodies have been isolated from the subject (human or non-human) they were raised in or obtained from a hybridoma supernatant, or may be engineered antibodies using sequences from the isolated antibodies.

[0096] The following examples are meant to illustrate, and are not intended to be limiting.

EXAMPLE 1

[0097] This example describes animal studies demonstrating an effect of anti-survivin antibodies on tumor growth.

[0098] Mice are administered DLAQMFFCFKELEGW- keyhole limpet hemocyanin (KLH) (SurVaxM) (SVN53-67/M57-KLH) (SEQ ID NO:4) as an immunization. Mice were injected subcutaneously with 100 μg of peptide. Mice were repeat immunized once every 7 days for a 28 day period. Two weeks after final immunization mice were euthanized via CO_2 asphyxiation and blood was collected through cardiac puncture. Blood was allowed to clot and is centrifuged at 10,000 x g to produce clarified serum. Survivin anti-serum was used to passively immunize mice in tumor implantation models.

[0099] Intracranial subcutaneous tumor models were used to show efficacy of anti-survivin antibody against tumor growth. Intracranial studies used anesthetized C57BL/6 mice implanted with 1 x 10^5 GL261 glioma cells through a 26 gauge needle advanced through an intracranial burr hole placed at 1mm anterior, 2 mm lateral and 3 mm in depth to the bregma skull suture as anatomical reference point. After 3 days mice were randomized into groups and injected with 10 μg of anti-survivin antibody or 10 μg of normal IgG for control. Antibodies were administered every 5 days for a total of 4 doses in a 20 day period. Mice were followed for signs of neurological deficits as an indicator of tumor growth and sacrificed according to established criteria. Data is represented as survival and shown in Kaplan-Meier plot, $p<0.0001$.

[0100] Subcutaneous tumor models were established through implantation of 1x10^6 GL261 glioma cells subcutaneously right flank through a 23 gauge intradermal needle. Tumors were allowed to grow for 7 days until they reached approximately 2 mm in diameter. Mice were then on day 7 administered 100 μg SurVaxM (SVN53-67/M57-KLH) survivin vaccine; or 50 μl anti-survivin antibody in the form of mouse sera from mice that had been previously administered SurVaxM or 10 μg mAb (antibody) derived from non-tumor bearing

pooled mice receiving the SurVaxM survivin vaccine, or a monoclonal antibody reactive against survivin. Treatment was re-administered every 7 days for 4 doses over a 28 day period. Tumors were measured daily and volumes calculated using the formula "V=XY2/2". Mice were followed for 60 days. Data is shown as combined tumor volumes (Figure 1) and individual tumor progression (Figure 2), $p<0.0001$. The SurVaxM vaccine refers to a vaccine in which the peptide has the sequence DLAQMFFCFKELEGW (SEQ ID NO: 4).

[0101] The results of these studies were as follows. As shown in Figure 1, in intracranial glioma model C57BL/6 mice with GL261 gliomas, who were administered anti-survivin antibody once every 7 days post tumor implantation, mice receiving anti-survivin antibody survived significantly longer than controls. IgG used is normal mouse non-specific IgG. Figure 2 shows subcutaneous tumor model in C57BL/6 mice with GL261 glioma. Mice were administered the indicated treatments once every 7 days post tumor implantation. Similar to intracranial studies, mice receiving either purified mAb or anti-serum had tumors that were significantly smaller than controls and rivaled the anti-tumor effect observed by the active vaccine itself. Figure 3 shows subcutaneous tumor model in C57BL/6 mice with GL261 glioma. Mice were administered the indicated treatments once every 7 days post tumor implantation. SurVaxM is the survivin vaccine; anti-survivin sera (antibody) was derived from non-tumor bearing pooled mice receiving active SurVaxM vaccine. Data shows individual tumor growth over 50 days. (n=4 per group)

[0102] These data demonstrate that administration of survivin antibodies are effective for reducing tumor volume and prolong survival.

EXAMPLE 2

[0103] This example describes the generation of monoclonal antibodies and the effectiveness of the antibodies for inhibiting tumor growth.

[0104] **Methods:**

[0105] **Cell lines and culture conditions:** GL261 murine glioma cells and B16f1 murine melanoma cell lines are grown on 100-mm tissue culture plates in complete Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum, 5,000 units penicillin/streptomycin, 50 μM 2-mercaptoethanol, 25mM HEPES, and 1x non-essential amino acids at 37°C in 5% CO_2 with media changes two to three times per week.

[0106] **Peptides:** Peptide synthesis was performed using Fmoc chemistry and a solid support resin (Genscript, Piscataway, NJ). Each peptide was stored at -20°C until use and diluted in DMSO. Antigen sequence 1: DLAQMFFCFKELEGW (SEQ ID NO:4); Antigen

sequence 2: DLAQCFFCFKELEGW (SEQ ID NO:27); Immunogen: Peptide (Lot: 614429-1)-KLH conjugate.

[0107] Immunization of mice for antibody production: Ten mice were used per round of antibody production. 5 Balb/c mice and 5 C57Bl/6 mice were used to produce anti-serum reactive against antigen 1 (SVN53-67/M57). Mice were immunized with Immunogen: Peptide -KLH conjugate (SVN53-67/M57-KLH). Serum samples were obtained after 4 rounds of immunization. Upon confirmation of survivin reactive anti-serum through indirect ELISA analysis, positive-testing mice were selected for hybridoma production. Several hybridoma cell lines were produced with cells from each reactive mouse fused to SP2/0 myeloma cells. Of these cell lines 2 subclones were further isolated and characterized.

[0108] Indirect ELISA for antibody reactivity: 96 well ELISA plates were coated with 1 μg/ml, 100 μl/well of either Coating Antigens: A: (SVN53-67/M57) DLAQMFFCFKELEGW (SEQ ID NO:4) or B: (wild type SVN53-67) DLAQCFFCFKELEGW (SEQ ID NO:27) in Phosphate Buffered Saline, pH 7.4. Murine anti-serum or hybridoma cell culture supernatant was applied 100ul/well to coated plates and incubated. Secondary Antibody: Peroxidase-AffiniPure Goat Anti-Mouse IgG, Fcγ was then added followed with standard detection.

[0109] Hybridoma sequencing: Total RNA was isolated from the hybridoma cells following the technical manual of TRIzol® Reagent (Ambion, Cat. No. : 15596-026). The total RNA was analyzed by agarose gel electrophoresis. Total RNA was reverse transcribed into cDNA using isotype-specific anti-sense primers or universal primers following the technical manual of PrimeScriptTM 1st Strand cDNA Synthesis Kit (Takara, Cat. No. : 6110A). The antibody fragments of VH and VL were amplified according to the standard operating procedure of RACE of GenScript. Amplified antibody fragments were separately cloned into a standard cloning vector using standard molecular cloning procedures. Colony PCR screening was performed to identify clones with inserts of correct sizes. No less than five single colonies with inserts of correct sizes were sequenced for each antibody fragment. Five single colonies with correct VH and VL insert sizes were sent for sequencing. The VH and VL genes of five different clones were found nearly identical. The consensus sequence is believed to be the sequence of the antibody produced.

[0110] Patient Serum Antibody Measurements: Patient serum was collected and stored at -80°C. Serial dilutions of clarified serum were applied to unconjugated survivin peptide, free KLH and random peptide (20μg/ml, 1μg/well) on pre-coated ELISA plates (Flat Bottom, Nunc) in triplicate. Samples were incubated at 4°C overnight and washed (PBS, 1%

BSA). HRP conjugated anti-human IgG detection antibody (Bio-Rad) was added for 1 hour at 25°C. Plates were washed 4 times and TMB colorimetric solution (Biolegend) was added at room temperature and developed for 15 minutes and read on a Bio-Rad automated plate reader at 450nm.

[0111] **Immunization of mice for tumor growth studies:** Proof of principle studies in mice were performed with 100µl of anti-SVN53-67/M57 hybridoma supernatant or 10µg of purified monoclonal antibody. Mice were first implanted with murine GL261 glioma cells or B16f1 murine melanoma cells either intracranially or subcutaneously. At four days post tumor implantation mice received i.p. injections of antibody repeated once weekly for a maximum of 5 weeks and followed for tumor growth.

[0112] **Intracerebral GL261 tumor cell injection and survival analysis:** Male C57BL/6 mice (Charles River, Horsham, PA) were anesthetized with gas isofluorane and fixed in a stereotactic head frame (David Kopf Instruments, Tujunga, CA). A midline scalp incision was made and the bregma was identified. Stereotactic coordinates were measured (2.0 mm lateral, and 1.2 mm anterior to the bregma) for implantation of cells into the deep frontal white matter. A burr hole was drilled at this point and 1 x 10^5 GL261 cells suspended in 2.5µl of DMEM were injected through a Hamilton syringe with a fixed, 25-gauge needle at a depth of 3.0 mm relative to the dura mater. Injections were performed at 1 µl/min. The needle was withdrawn and the incision sutured. Kaplan–Meier survival plots were drawn and median survival times were determined for all groups. n=8 mice per group.

[0113] **Subcutaneous tumor growth studies:** A suspension of 2 x 10^7 Gl261 cells or 1 x 10^6 B16f1 cells in 100µl of PBS was injected into the shaved right flank subcutaneous skin of male C57Bl/6 (immunocompetent) mice (Charles River, Horsham, PA) as well as Nude (immunocompromised) NCr -nu/nu mice (Charles River, Horsham, PA) . Tumor growth was measured daily with calipers, and volumes were calculated according to the formula $V=(a\cdot(b^2))/2$, where V is volume and a and b are perpendicular diameters of the tumor. Data is presented as tumor growth over time as well as comparative mean tumor volumes. n = 4, 5 or 10 mice per group in various studies presented as indicated.

[0114] **Results:**

[0115] A modified survivin peptide of SEQ ID NO: 4 was used to generate hybridomas. Ten mice were administered 15 µg/ml peptide vaccine comprising the peptide of SEQ ID NO:4. Out of these 9 mice developed anti-survivin titers. Several hybridoma lines were genrated which produced antibodies that were reactive against peptide of SEQ ID NO:4

and a survivin peptide DLAQCFFCFKELEGW (SEQ ID NO:27) in which the sequence is identifical to a portion of human survivin. Out of the hybridomas, two in particular were selected for further characterization. These are termed as 2C2 and the 30H3. From these hybridomas, one clone each was further characterized. These are termed as 2C2E7 and 30H3D2 respectively. 2C2E7 was found to have the isotype IgG2b and 30H3D2 was found to have the isotype IgG1. Therefore, A few single colonies with correct heavy and light chain variable region insert sizes were sequenced. The sequences were found to be nearly identical and consensus sequences were generated. Consensus amino acid sequence for the heavy and light chain variable regions from the mAb 2C2E7 are provided in SEQ ID NOs:19 and 20 respectively. Consensus amino acid sequence for the heavy and light chain variable regions from the mAb 30H3D2 are provided in SEQ ID NOs:21 and 22 respectively. The corresponding nucleotide sequences for the amino acid sequences of SEQ ID NOs:19, 20, 21 and 22 are provided in SEQ ID NOs:23, 24, 25 and 26 respectively.

[0116] The consensus amino acid sequence for heavy chain variable region from antibody 2C2E7 is shown below:

MGWLWNLLFLMAAAQSAQAQIQLVQSGPELKKPGETVKISCKASGYTFTTYGMSW VKQAPGRGLKWMGWINPYSGVPTYAVDFKGRFAFSLETSASTAYLQINNLKNEDTA TYFCARGGRRGDFGYWGQGTTLTVSS (SEQ ID NO:19).

[0117] The consensus amino acid sequence for light chain variable region from antibody 2C2E7 is shown below:

MDFQVQIFSFLLISASVILSSGQIGLTQSPAIMSASPGEKVTMTCSASSSISYMHWYQQ KPGTSPKTWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCHQRSSHHT FGGGTKLEIK (SEQ ID NO:20).

[0118] The consensus amino acid sequence for heavy chain variable region from antibody 30H3D2 is shown below:

MNFGLSLIFLALILKGVQCEVQLVESGGDLVKPGGSLKLSCAASGFTFSSYGMSWVR LTPDKRLEWVATISSGGSHTYYPDSVRGRFTISRDNAKNTLYLQMSSLKSEDTAMYY CARHPIYYYISSYAMDYWGQGTSVTVSS (SEQ ID NO:21).

[0119] The consensus amino acid sequence for light chain variable region from antibody 30H3D2 is shown below:

MKLPVRLLVLMFWIPASSSDVVMTQTPLSLPVSLGDQASISCRSSQSLVHSTGNTYLH WYLQKPGQSPKLLIYKVSNRFSGVPDRFGGSGSGTDFTLKISRVEAEDLGVYFCSQST HVPPTFGGGTKLEIK (SEQ ID NO:22).

[0120] A nucleotide sequence encoding the amino acids of heavy chain variable domain set forth in SEQ ID NO:19 of mAb 2C2E7 is shown below:

ATGGGTTGGCTGTGGAACTTGCTATTCCTGATGGCAGCTGCCCAAAGTGCCCAAG
CACAGATCCAGTTGGTACAATCTGGACCTGAGCTGAAGAAGCCTGGAGAGACAG
TCAAGATCTCCTGCAAGGCTTCTGGGTATACCTTCACAACCTATGGAATGAGCTG
GGTGAAACAGGCTCCAGGAAGGGGTTTAAAGTGGATGGGCTGGATAAACCCCTA
CTCTGGAGTGCCAACATATGCTGTTGACTTCAAGGGACGGTTTGCCTTCTCTTTGG
AAACCTCTGCCAGCACTGCCTATTTGCAGATCAACAACCTCAAAAATGAGGACA
CGGCTACATATTTCTGTGCAAGAGGAGGGCGGAGGGGGGACTTTGGCTACTGGG
GCCAAGGCACCACTCTCACAGTCTCCTCA (SEQ ID NO:23).

[0121] A nucleotide sequence encoding the amino acids of light chain variable domain set forth in SEQ ID NO:20 of mAb 2C2E7 is shown below:

ATGGATTTTCAGGTGCAGATTTTCAGCTTCCTGCTAATCAGTGCCTCAGTCATACT
GTCCAGCGGACAAATTGGTCTCACCCAGTCTCCAGCAATCATGTCTGCATCTCCA
GGGGAGAAGGTCACCATGACCTGCAGTGCCAGCTCAAGTATAAGTTACATGCAT
TGGTACCAGCAGAAGCCAGGCACCTCCCCCAAAACATGGATTTATGACACATCC
AAACTGGCTTCTGGAGTCCCTGCTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTT
ATTCTCTCACAATCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATTACTGCCA
TCAGCGGAGTAGTCACCACACGTTCGGAGGGGGGACCAAGCTGGAAATAAAA
(SEQ ID NO:24).

[0122] A nucleotide sequence encoding the amino acids of heavy chain variable domain set forth in SEQ ID NO:21 of mAb 30H3D2 is shown below:

ATGAACTTCGGGCTCAGCTTGATTTTCCTTGCCCTTATTTTAAAAGGTGTCCAGTG
TGAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTAGTGAAGCCTGGAGGGTCCCT
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GGTAGTCACACCTACTATCCAGACAGTGTGAGGGGGCGATTCACCATCTCCAGA
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ACAGCCATGTATTACTGTGCAAGACACCCAATTTATTACTACATTAGTAGCTATG
CTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA (SEQ ID NO:25).

[0123] A nucleotide sequence encoding the amino acids of light chain variable domain set forth in SEQ ID NO:22 of mAb 30H3D2 is shown below:

ATGAAGTTGCCTGTTAGGCTGTTGGTGCTGATGTTCTGGATTCCTGCTTCCAGCAG
TGATGTTGTGATGACCCAAACTCCACTCTCCCTGCCTGTCAGTCTTGGAGATCAA

GCCTCCATCTCTTGCAGATCTAGTCAGAGCCTTGTACACAGTACTGGAAACACCT
ATTTACATTGGTACCTGCAGAAGCCAGGCCAGTCTCCAAAGCTCCTGATCTACAA
AGTTTCCAACCGATTTTCTGGGGTCCCAGACAGGTTCGGTGGCAGTGGATCAGGG
ACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATCTGGGAGTTTAT
TTCTGCTCTCAAAGTACACATGTTCCTCCGACGTTCGGTGGAGGCACCAAGCTGG
AAATCAAA (SEQ ID NO:26).

[0124] The antibodies were tested for binding against the peptide used for immunizing the animals (SEQ ID NO:4), and against a sequence from human survivin (SEQ ID NO:27). 15 ng/ml antibody concentration of 2C2E7 was sufficient to bind the modified survivin peptide of SEQ ID NO:4 at an OD of 1.019 and wild type survivin peptide of SEQ ID NO:27 at an OD of 0.891. The titer of 2C2E7 at its highest dilution with signal to blank ratio of >2:1 is 1:512,000 consistent with that expected for a high affinity antibody. Further, 31 ng/ml antibody concentration of 30H3D2 was sufficient to bind the modified survivin peptide of SEQ ID NO:4 at an OD of 1.021 and wild type survivin peptide of SEQ ID NO:27 at an OD of 0.874. The titer of 30H3 at its highest dilution with signal to blank ratio of >2:1 is 1:512,000 is consistent with that expected for a high affinity antibody.

[0125] The antibodies were then used in animal models to determine the effect of growth of tumors. The animal models were same as used in Example 1. The results are shown in Figures 4 to 11. Studies of 2C2 and H30 anti-survivin antibodies were perfromed in subcutaneous murine tumor models. Mice were allowed to establish an implantable tumor after which they began treatment with 2C2, H30 or non-specific IgG every 5-7 days for a 30 day period. Two host mouse strains were used, NCr-nu/nu (nude) in Figures 4, 6, 8, 10 and C57Bl/6 mice in Figures 5, 7, 9, 11. Nude mice represent an immunocompromised model in which activity of antibodies would be expected to specifically depend on direct antibody binding to target without immune system support. C57Bl/6 mice represent an immunocompetent model where antibodies may benefit from the additional engagement of immunological support mechanisms such as Macrophages, Dendritic cells and T cells. B16 melanoma Figures 4-7 and GL261 glioma cells Figures 8-11 were shown to be growth inhibited in the C57Bl/6 (immunocompetent) model (Figures 5, 7) and to a lesser extent also growth inhibited in the nude (immunocompromised) model (Figures 4, 6) when treated with 2C2 or H30 antibodies. This observation shows a strong immune-mediated antibody-dependent response in C57Bl/6 mice (Figures 5, 7, 9, 11) that is not completely abrogated by the lack of immune support in Nude mice (Figures 4, 6, 8, 10). In immunocompromised models (Figures 4, 6, 8, 10) the persistance of antibody-dependent growth inhibition strongly

suggests an added immune system independent or direct growth inhibitory component of antibody by itself. Glioma patients enrolled in a Phase I clinical trial at Roswell Park Cancer Institute of SurVaxM (SVN53-67/M57-KLH) SEQ. ID NO:4 (FDA approved/I171010) were observed to produce an unexpected antibody response to the SurVaxM peptide during their clinical trial protocol period. Eight patients shown here produce a reactive anti-sera that is cross reactive to both wild type survivin peptide comprised of amino acids of SEQ ID NO:27 as well as the modified survivin peptide comprised of amino acids of SEQ ID NO:4 which is also contained in the 15 amino acid immunizing peptide sequence. These antibodies can be used for therapeutic purposes.

[0126] Although the present disclosure has been described using specific embodiments and examples, routine modifications will be apparent to those skilled in the art and such modifications are intended to be within the scope of the disclosure and the claims.

[0127] The term “comprise” and variants of the term such as “comprises” or “comprising” are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[0128] Any reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

Claims:

1. A method for treating survivin-expressing tumor in an individual comprising administering a composition to the individual who has survivin-expressing tumor, said composition comprising an antibody that is specific for survivin, wherein the antibody comprises a heavy chain variable region and light chain variable region, wherein,

a) the heavy chain variable region comprises a VH CDR1 comprising the sequence of SEQ ID NO:7, a VH CDR2 comprising the sequence of SEQ ID NO:8, and a VH CDR3 comprising the sequence of SEQ ID NO:9, and the light chain variable region comprises a VL CDR1 comprising the sequence of SEQ ID NO:10, a VL CDR2 comprising the sequence of SEQ ID NO:11, and a VL CDR3 comprising the sequence of SEQ ID NO:12; or

b) the heavy chain variable region comprises a VH CDR1 comprising the sequence of SEQ ID NO:13, a VH CDR2 comprising the sequence of SEQ ID NO:14, and a VH CDR3 comprising the sequence of SEQ ID NO:15, and the light chain variable region comprises a VL CDR1 comprising the sequence of SEQ ID NO:16, a VL CDR2 comprising the sequence of SEQ ID NO:17, and a VL CDR3 comprising the sequence of SEQ ID NO:18.

2. The method of claim 1, wherein the antibody has been generated in response to a peptide which is 9 to 23 amino acids long and comprises the sequence QMFFCF (SEQ ID NO:3).

3. The method of claim 2, wherein the antibody has been generated in response to a peptide which has the sequence DLAQMFFCFKELEGW (SEQ ID NO:4).

4. The method of claim 1, wherein the antibody is a monoclonal or a polyclonal antibody.

5. The method of claim 1, wherein the antibody is a chimeric antibody, a humanized antibody, a human antibody, a single chain antibody, a bispecific antibody or a multispecific antibody.

6. The method of claim 1, wherein the antibody has an isotype IgG1, IgG2, IgG3, IgG4, IgM, IgA, IgD or IgE.

7. The method of claim 6, wherein the antibody has an isotype of IgG2b or IgG1.

8. The method of claim 1, wherein the heavy chain variable region comprises an amino acid sequence having at least a 90% sequence identity to SEQ ID NO:19 and the light chain variable region comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:20.

9. The method of claim 1, wherein the heavy chain variable region comprises an amino acid sequence having at least a 90% sequence identity to SEQ ID NO:21 and the light chain variable region comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:22.

10. An isolated monoclonal antibody that specifically binds to survivin comprising a heavy chain variable region and light chain variable region, wherein,

a) the heavy chain variable region comprises a VH CDR1 comprising the sequence of SEQ ID NO: 7, a VH CDR2 comprising the sequence of SEQ ID NO: 8, and a VH CDR3 comprising the sequence of SEQ ID NO: 9, and the light chain variable region comprises a VL CDR1 comprising the sequence of SEQ ID NO: 10, a VL CDR2 comprising the sequence of SEQ ID NO: 11, and a VL CDR3 comprising the sequence of SEQ ID NO: 12; or

b) the heavy chain variable region comprises a VH CDR1 comprising the sequence of SEQ ID NO:13, a VH CDR2 comprising the sequence of SEQ ID NO:14, and a VH CDR3 comprising the sequence of SEQ ID NO:15, and the light chain variable region comprises a VL CDR1 comprising the sequence of SEQ ID NO:16, a VL CDR2 comprising the sequence of SEQ ID NO:17, and a VL CDR3 comprising the sequence of SEQ ID NO:18.

11. The antibody of claim 10, wherein the heavy chain variable region comprises an amino acid sequence having at least a 90% sequence identity to SEQ ID NO:19 and the light chain variable region comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 20.

12. The antibody of claim 10, wherein the heavy chain variable region comprises an amino acid sequence having at least a 90% sequence identity to SEQ ID NO: 21 and the light chain variable region comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 22.

13. The antibody of claim 10, wherein the antibody is a chimeric antibody, a humanized antibody, a human antibody, a single chain antibody, a bispecific antibody or a multispecific antibody.

14. The antibody of claim 10, wherein the antibody has an isotype IgG1, IgG2, IgG3, IgG4, IgM, IgA, IgD or IgE.

15. The antibody of claim 14, wherein the antibody has an isotype of IgG2b or IgG1.

16. A pharmaceutical composition comprising the antibody of claim 10 and a pharmaceutically acceptable carrier.

17. A hybridoma cell producing the monoclonal antibody of claim 10.

18. The hybridoma cell of claim 17, wherein the monoclonal antibody is of isotype IgG2b or IgG1.

19. A transformed cell into which has been introduced a polynucleotide sequence encoding the sequence of SEQ ID NOs: 7 to 12, or of SEQ ID NOs: 13 to 18.

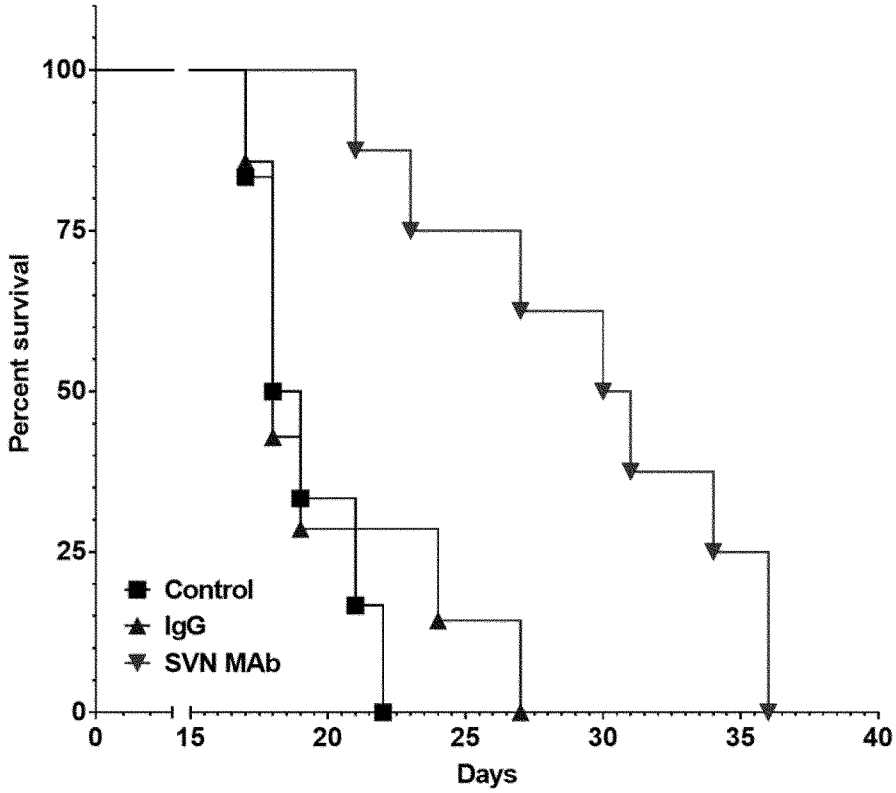
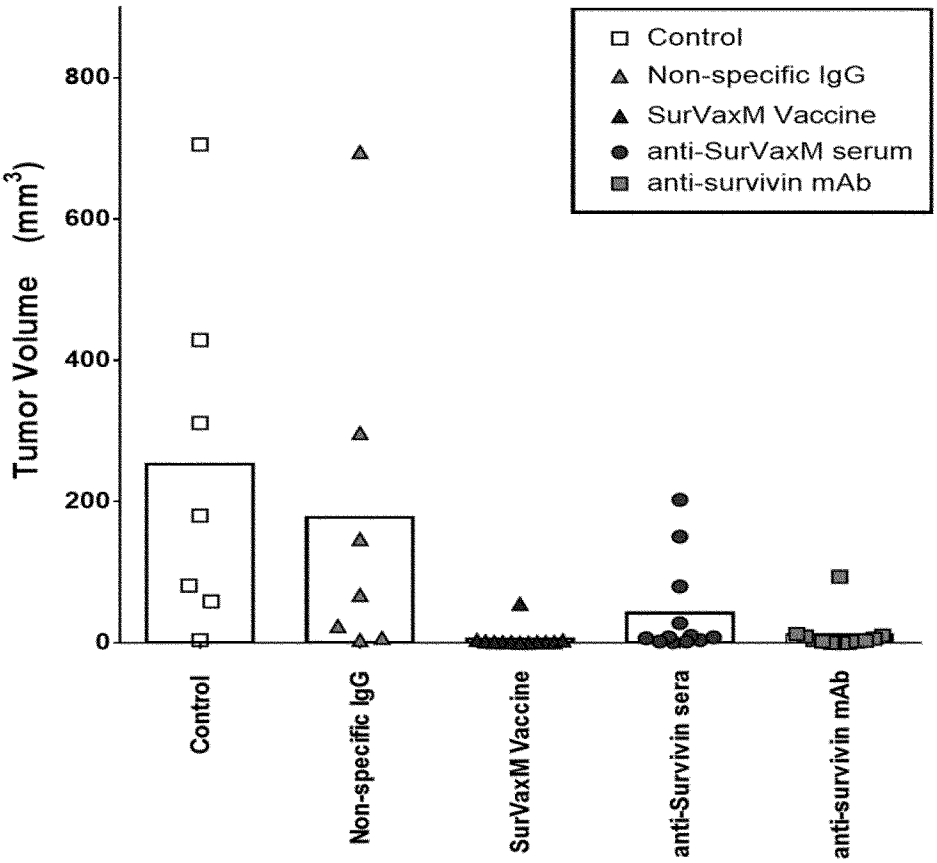


Figure 1



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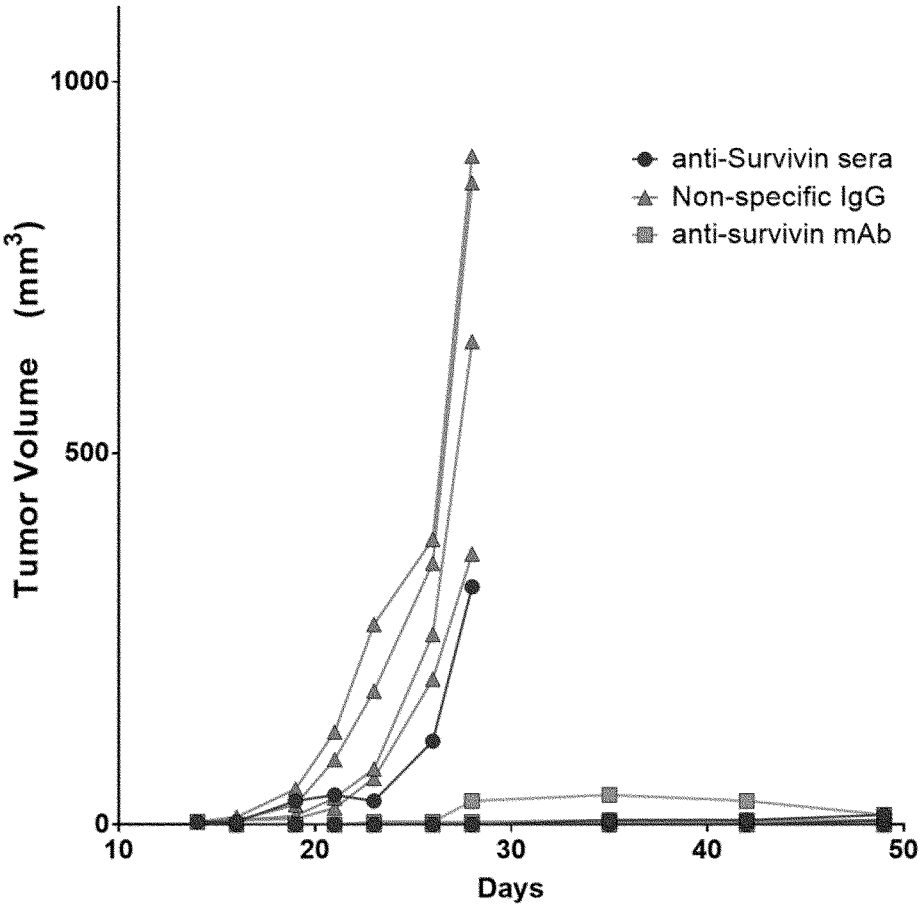
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500
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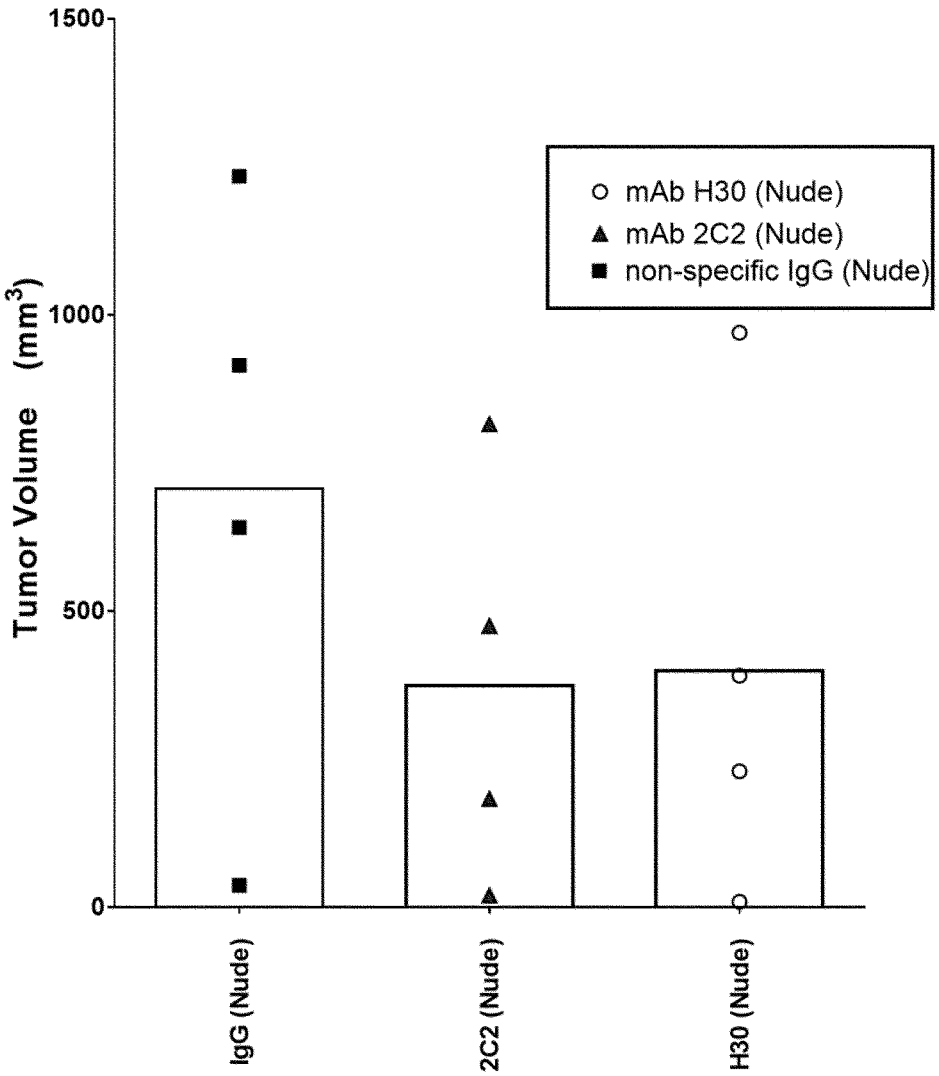
Tumor Volume (mm3)
10
20
30
40
50
Days
anti-Survivin sera
Non-specific IgG
anti-survivin mAb

Figure 3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500
0
Tumor Volume (mm3)
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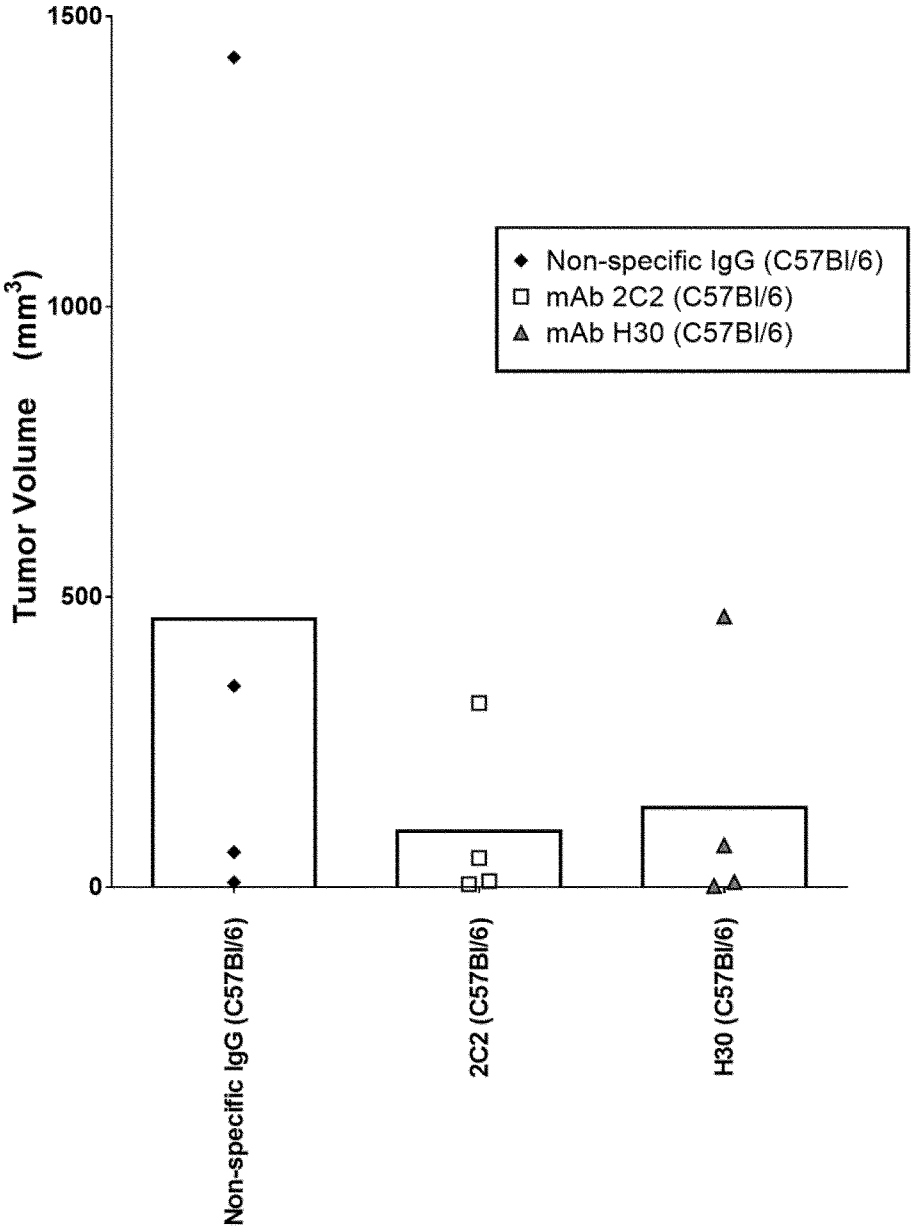
mAb 2C2 (Nude)
non-specific IgG (Nude)
IgG (Nude)
2C2 (Nude)
H30 (Nude)

Figure 4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500
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Tumor Volume (mm3)
Non-specific IgG (C57Bl/6)
mAb 2C2 (C57Bl/6)
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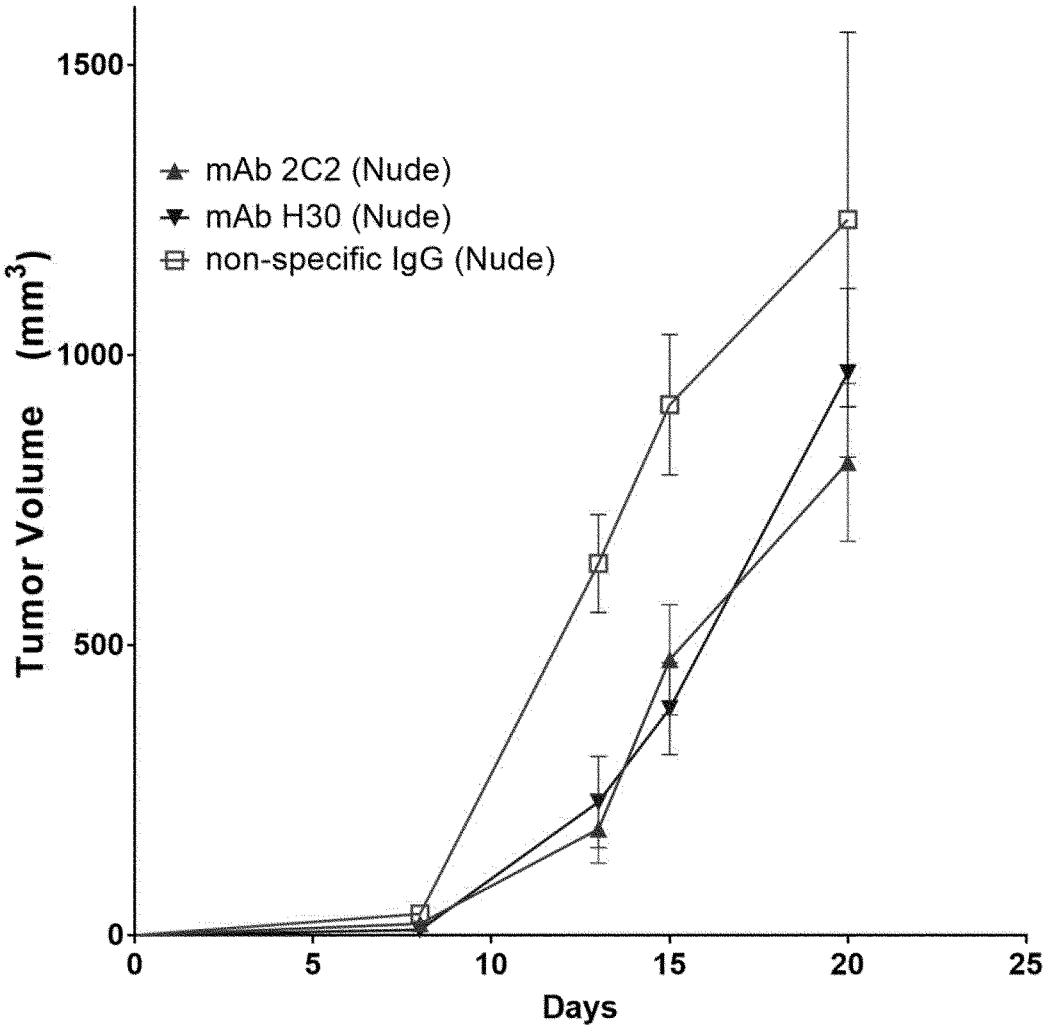
Non-specific IgG (C57Bl/6)
2C2 (C57Bl/6)
H30 (C57Bl/6)

Figure 5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Tumor Volume (mm3)
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non-specific IgG (Nude)
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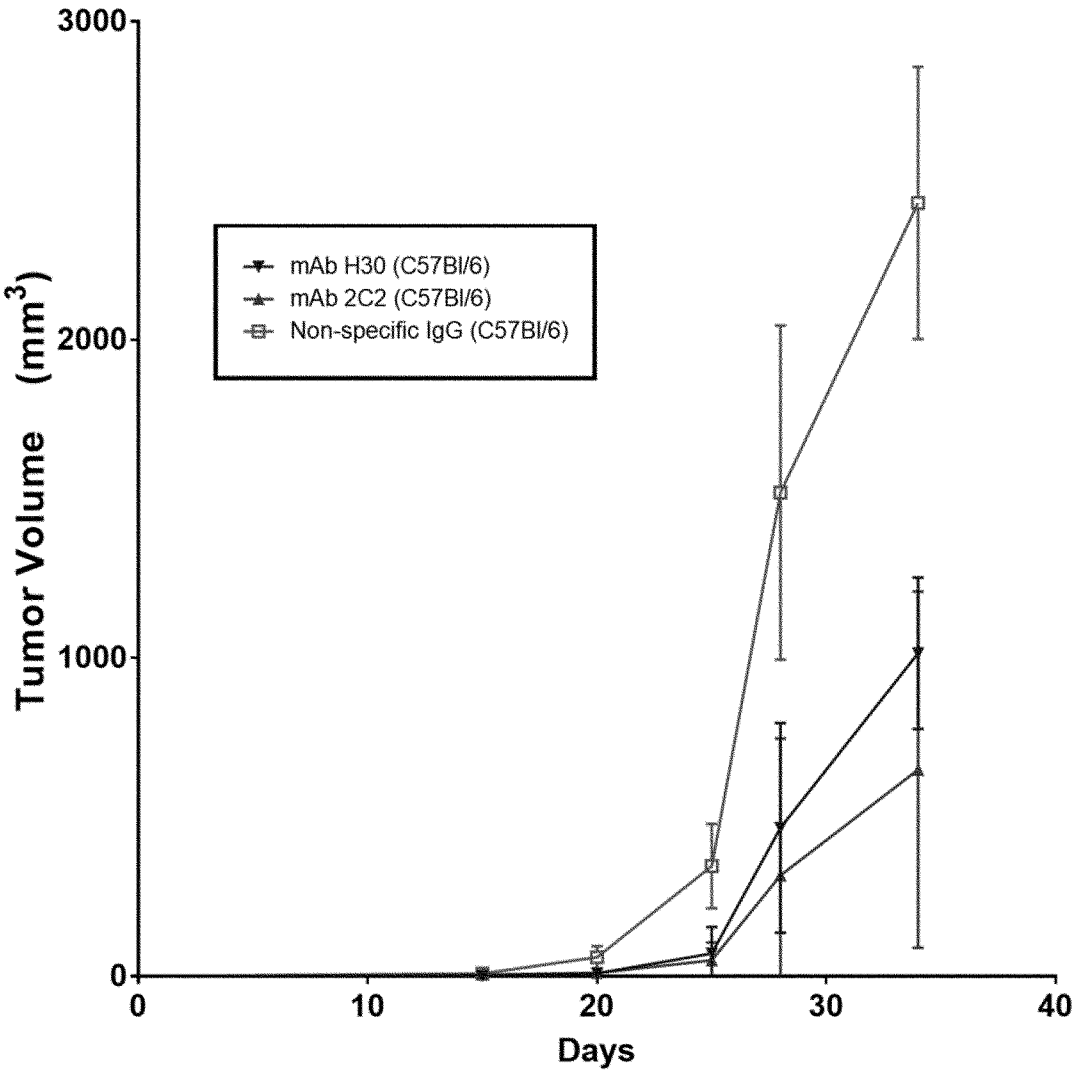
5
10
15
20
25
Days

Figure 6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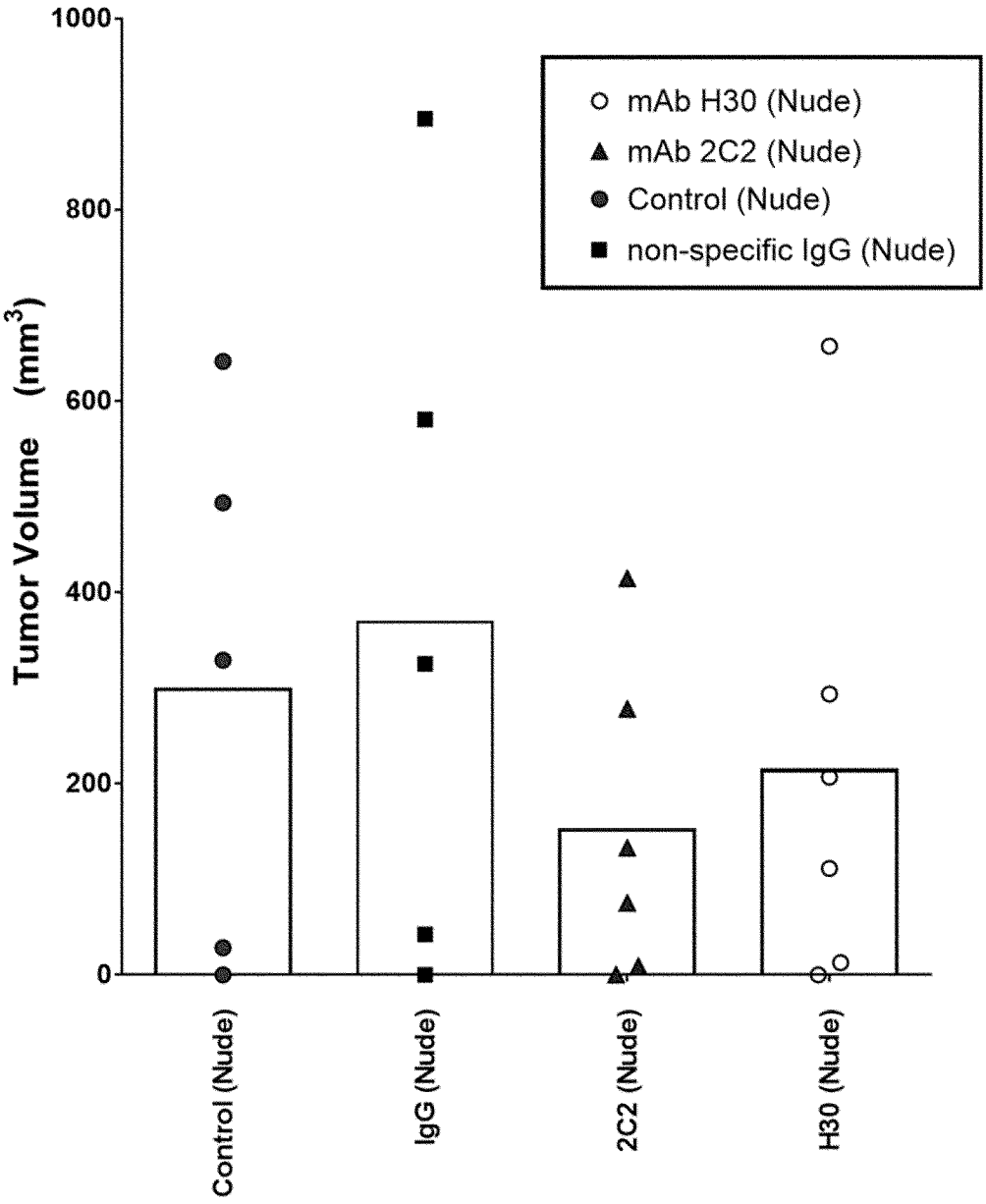
2000
1000
0
Tumor Volume (mm3)
0
10
20
30
40
Days
mAb H30 (C57Bl/6)
mAb 2C2 (C57Bl/6)
Non-specific IgG (C57Bl/6)

Figure 7


1000
800
600
400
200
0
Tumor Volume (mm3)
mAb H30 (Nude)
mAb 2C2 (Nude)
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non-specific IgG (Nude)
Control (Nude)
IgG (Nude)
2C2 (Nude)
H30 (Nude)

Figure 8

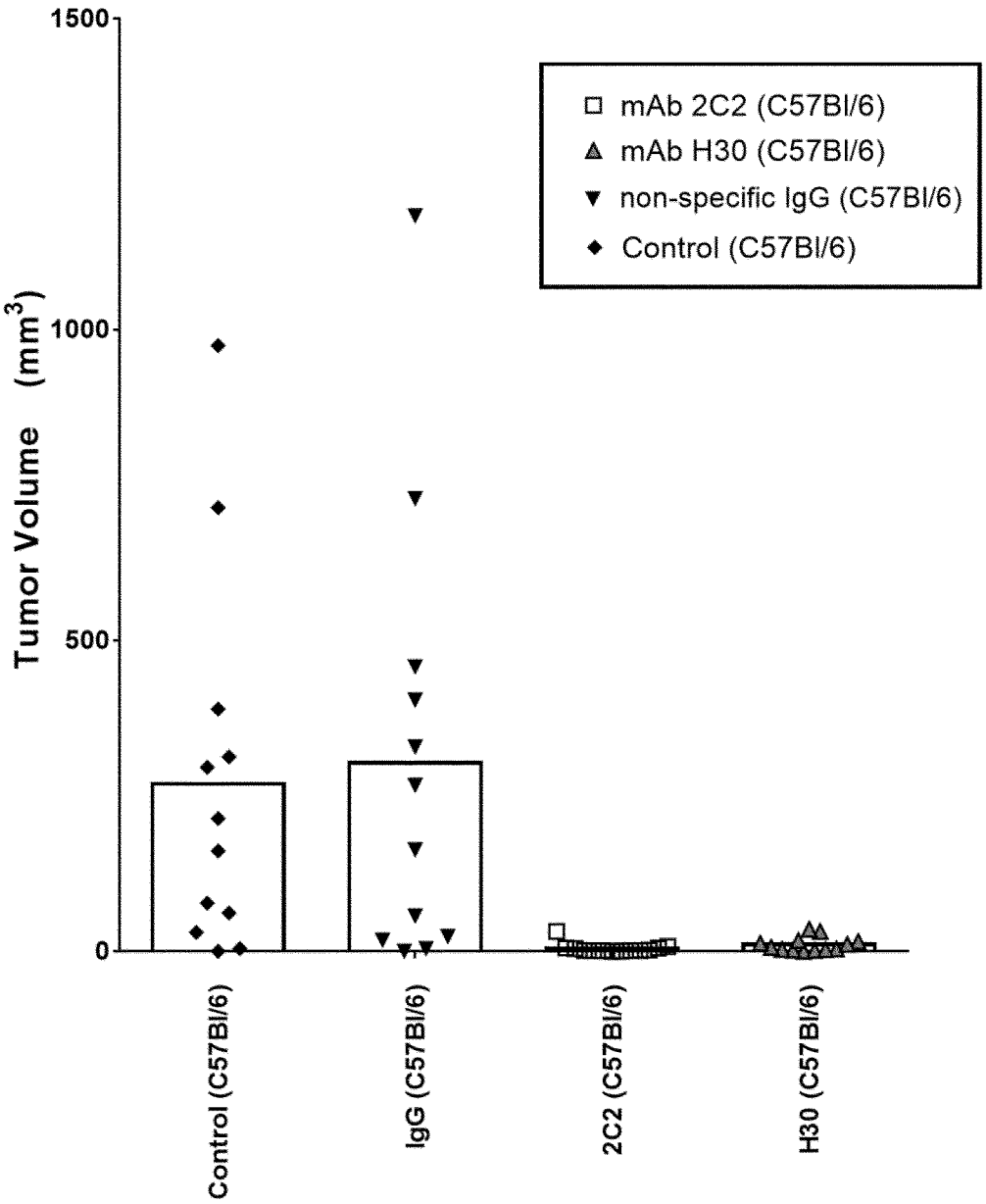

1500
1000
500
0
Tumor Volume (mm3)
mAb 2C2 (C57Bl/6)
mAb H30 (C57Bl/6)
non-specific IgG (C57Bl/6)
Control (C57Bl/6)
Control (C57Bl/6)
IgG (C57Bl/6)
2C2 (C57Bl/6)
H30 (C57Bl/6)

Figure 9

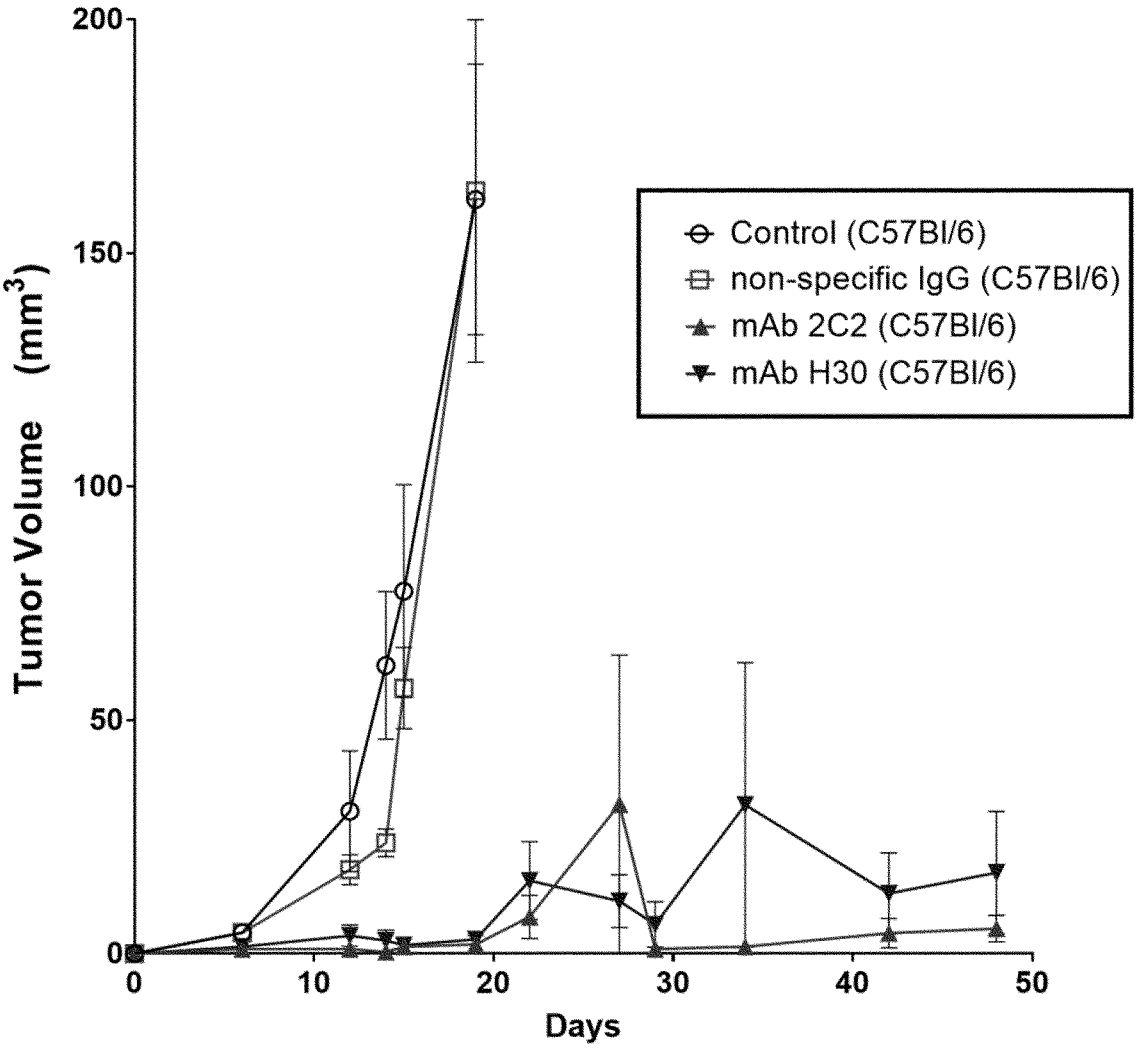

Tumor Volume (mm3)
200
150
100
50
0
0
10
20
30
40
50
Days
Control (C57Bl/6)
non-specific IgG (C57Bl/6)
mAb 2C2 (C57Bl/6)
mAb H30 (C57Bl/6)

Figure 10

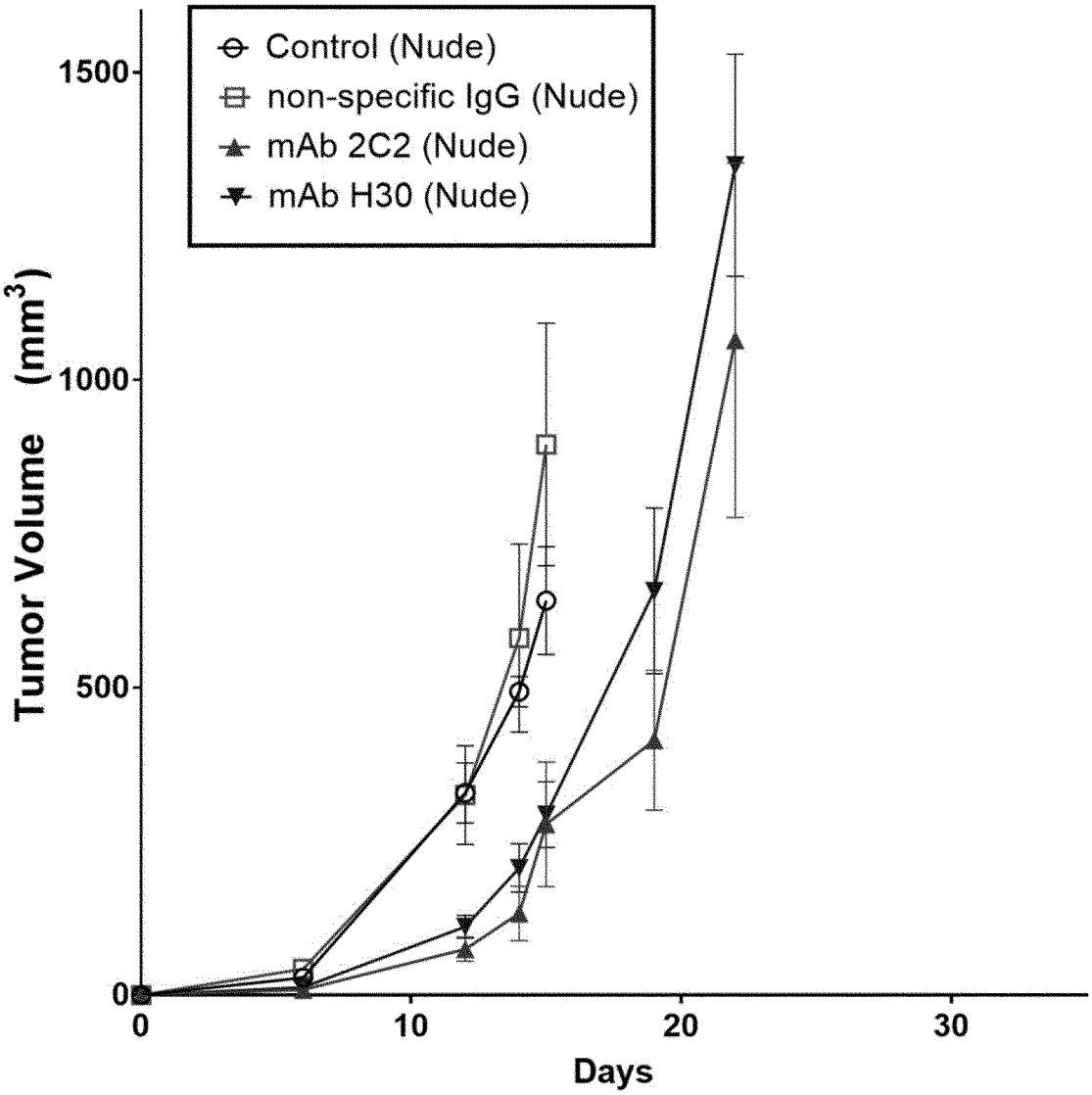
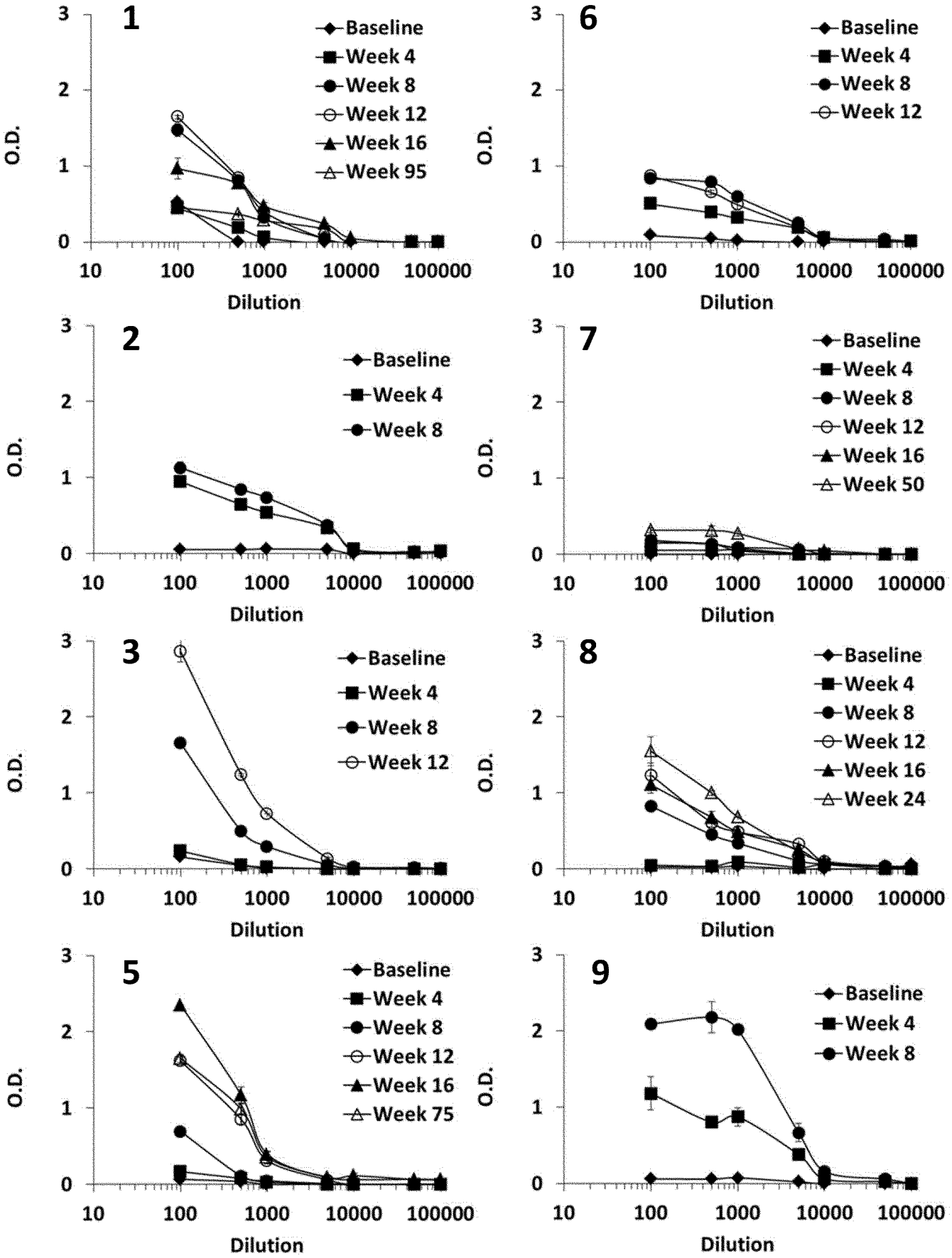

Control (Nude)
non-specific IgG (Nude)
mAb 2C2 (Nude)
mAb H30 (Nude)
Tumor Volume (mm3)
1500
1000
500
0
0
10
20
30
Days

Figure 11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Week 12
Week 16
Week 95
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Week 4
Week 8
Week 12
Week 16
Week 50
3
Baseline
Week 4
Week 8
Week 12
8
Baseline
Week 4
Week 8
Week 12
Week 16
Week 24
5
Baseline
Week 4
Week 8
Week 12
Week 16
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Dilution
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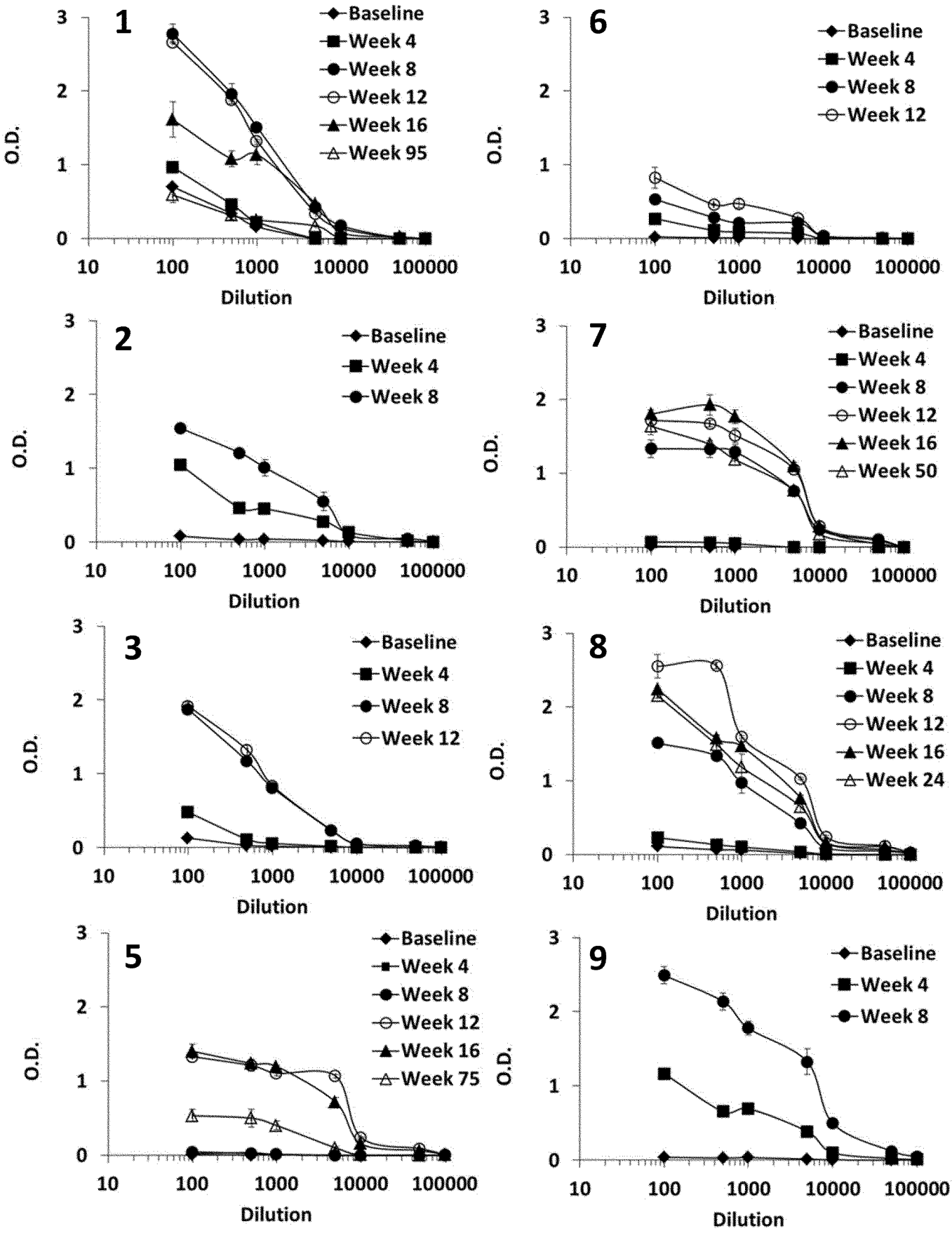
Figure 12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Week 8
7
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Week 4
Week 8
Week 12
Week 16
Week 50
3
Baseline
Week 4
Week 8
Week 12
8
Baseline
Week 4
Week 8
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Baseline
Week 4
Week 8

Figure 13

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Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Cys Asp Asn Pro Tyr Ile
            260                 265                 270

cca aat ggt gac tac tca cct tta agg att aaa cac aga act gga gat        864
Pro Asn Gly Asp Tyr Ser Pro Leu Arg Ile Lys His Arg Thr Gly Asp
        275                 280                 285

gaa atc acg tac cag tgt aga aat ggt ttt tat cct gca acc cgg gga        912
Glu Ile Thr Tyr Gln Cys Arg Asn Gly Phe Tyr Pro Ala Thr Arg Gly
    290                 295                 300

aat aca gcc aaa tgc aca agt act ggc tgg ata cct gct ccg aga tgt        960
Asn Thr Ala Lys Cys Thr Ser Thr Gly Trp Ile Pro Ala Pro Arg Cys
305                 310                 315                 320

acc ttg aaa cct tgt gat tat cca gac att aaa cat gga ggt cta tat       1008
Thr Leu Lys Pro Cys Asp Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr
                325                 330                 335

cat gag aat atg cgt aga cca tac ttt cca gta gct gta gga aaa tat       1056
His Glu Asn Met Arg Arg Pro Tyr Phe Pro Val Ala Val Gly Lys Tyr
            340                 345                 350

tac tcc tat tac tgt gat gaa cat ttt gag act ccg tca gga agt tac       1104
Tyr Ser Tyr Tyr Cys Asp Glu His Phe Glu Thr Pro Ser Gly Ser Tyr
        355                 360                 365
```

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tgg gat cac att cat tgc aca caa gat gga tgg tcg cca gca gta cca       1152
Trp Asp His Ile His Cys Thr Gln Asp Gly Trp Ser Pro Ala Val Pro
    370                 375                 380

tgc ctc aga aaa tgt tat ttt cct tat ttg gaa aat gga tat aat caa       1200
Cys Leu Arg Lys Cys Tyr Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln
385                 390                 395                 400

aat tat gga aga aag ttt gta cag ggt aaa tct ata gac gtt gcc tgc       1248
Asn Tyr Gly Arg Lys Phe Val Gln Gly Lys Ser Ile Asp Val Ala Cys
                405                 410                 415

cat cct ggc tac gct ctt cca aaa gcg cag acc aca gtt aca tgt atg       1296
His Pro Gly Tyr Ala Leu Pro Lys Ala Gln Thr Thr Val Thr Cys Met
            420                 425                 430

gag aat ggc tgg tct cct act ccc aga tgc atc cgt gtc aaa aca tgt       1344
Glu Asn Gly Trp Ser Pro Thr Pro Arg Cys Ile Arg Val Lys Thr Cys
        435                 440                 445

tcc aaa tca agt ata gat att gag aat ggg ttt att tct gaa tct cag       1392
Ser Lys Ser Ser Ile Asp Ile Glu Asn Gly Phe Ile Ser Glu Ser Gln
    450                 455                 460

tat aca tat gcc tta aaa gaa aaa gca aaa tat caa tgc aaa cta gga       1440
Tyr Thr Tyr Ala Leu Lys Glu Lys Ala Lys Tyr Gln Cys Lys Leu Gly
465                 470                 475                 480

tat gta aca gca gat ggt gaa aca tca gga tca att aca tgt ggg aaa       1488
Tyr Val Thr Ala Asp Gly Glu Thr Ser Gly Ser Ile Thr Cys Gly Lys
                485                 490                 495

gat gga tgg tca gct caa ccc acg tgc att aaa tct tgt gat atc cca       1536
Asp Gly Trp Ser Ala Gln Pro Thr Cys Ile Lys Ser Cys Asp Ile Pro
            500                 505                 510

gta ttt atg aat gcc aga act aaa aat gac ttc aca tgg ttt aag ctg       1584
Val Phe Met Asn Ala Arg Thr Lys Asn Asp Phe Thr Trp Phe Lys Leu
        515                 520                 525

aat gac aca ttg gac tat gaa tgc cat gat ggt tat gaa agc aat act       1632
Asn Asp Thr Leu Asp Tyr Glu Cys His Asp Gly Tyr Glu Ser Asn Thr
    530                 535                 540

gga agc acc act ggt tcc ata gtg tgt ggt tac aat ggt tgg tct gat       1680
Gly Ser Thr Thr Gly Ser Ile Val Cys Gly Tyr Asn Gly Trp Ser Asp
545                 550                 555                 560

tta ccc ata tgt tat gaa aga gaa tgc gaa ctt cct aaa ata gat gta       1728
Leu Pro Ile Cys Tyr Glu Arg Glu Cys Glu Leu Pro Lys Ile Asp Val
                565                 570                 575

cac tta gtt cct gat cgc aag aaa gac cag tat aaa gtt gga gag gtg       1776
His Leu Val Pro Asp Arg Lys Lys Asp Gln Tyr Lys Val Gly Glu Val
            580                 585                 590

ttg aaa ttc tcc tgc aaa cca gga ttt aca ata gtt gga cct aat tcc       1824
Leu Lys Phe Ser Cys Lys Pro Gly Phe Thr Ile Val Gly Pro Asn Ser
        595                 600                 605

gtt cag tgc tac cac ttt gga ttg tct cct gac ctc cca ata tgt aaa       1872
Val Gln Cys Tyr His Phe Gly Leu Ser Pro Asp Leu Pro Ile Cys Lys
    610                 615                 620
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gag caa gta caa tca tgt ggt cca cct cct gaa ctc ctc aat ggg aat       1920
Glu Gln Val Gln Ser Cys Gly Pro Pro Pro Glu Leu Leu Asn Gly Asn
625                 630                 635                 640

gtt aag gaa aaa acg aaa gaa gaa tat gga cac agt gaa gtg gtg gaa       1968
Val Lys Glu Lys Thr Lys Glu Glu Tyr Gly His Ser Glu Val Val Glu
                645                 650                 655

tat tat tgc aat cct aga ttt cta atg aag gga cct aat aaa att caa       2016
Tyr Tyr Cys Asn Pro Arg Phe Leu Met Lys Gly Pro Asn Lys Ile Gln
            660                 665                 670

tgt gtt gat gga gag tgg aca act tta cca gtg tgt att gtg gag gag       2064
Cys Val Asp Gly Glu Trp Thr Thr Leu Pro Val Cys Ile Val Glu Glu
        675                 680                 685

agt acc tgt gga gat ata cct gaa ctt gaa cat ggc tgg gcc cag ctt       2112
Ser Thr Cys Gly Asp Ile Pro Glu Leu Glu His Gly Trp Ala Gln Leu
    690                 695                 700

tct tcc cct cct tat tac tat gga gat tca gtg gaa ttc aat tgc tca       2160
Ser Ser Pro Pro Tyr Tyr Tyr Gly Asp Ser Val Glu Phe Asn Cys Ser
705                 710                 715                 720

gaa tca ttt aca atg att gga cac aga tca att acg tgt att cat gga       2208
Glu Ser Phe Thr Met Ile Gly His Arg Ser Ile Thr Cys Ile His Gly
                725                 730                 735

gta tgg acc caa ctt ccc cag tgt gtg gca ata gat aaa ctt aag aag       2256
Val Trp Thr Gln Leu Pro Gln Cys Val Ala Ile Asp Lys Leu Lys Lys
            740                 745                 750

tgc aaa tca tca aat tta att ata ctt gag gaa cat tta aaa aac aag       2304
Cys Lys Ser Ser Asn Leu Ile Ile Leu Glu Glu His Leu Lys Asn Lys
        755                 760                 765

aag gaa ttc gat cat aat tct aac ata agg tac aga tgt aga gga aaa       2352
Lys Glu Phe Asp His Asn Ser Asn Ile Arg Tyr Arg Cys Arg Gly Lys
    770                 775                 780

gaa gga tgg ata cac aca gtc tgc ata aat gga aga tgg gat cca gaa       2400
Glu Gly Trp Ile His Thr Val Cys Ile Asn Gly Arg Trp Asp Pro Glu
785                 790                 795                 800

gtg aac tgc tca atg gca caa ata caa tta tgc cca cct cca cct cag       2448
Val Asn Cys Ser Met Ala Gln Ile Gln Leu Cys Pro Pro Pro Pro Gln
                805                 810                 815

att ccc aat tct cac aat atg aca acc aca ctg aat tat cgg gat gga       2496
Ile Pro Asn Ser His Asn Met Thr Thr Thr Leu Asn Tyr Arg Asp Gly
            820                 825                 830

gaa aaa gta tct gtt ctt tgc caa gaa aat tat cta att cag gaa gga       2544
Glu Lys Val Ser Val Leu Cys Gln Glu Asn Tyr Leu Ile Gln Glu Gly
        835                 840                 845

gaa gaa att aca tgc aaa gat gga aga tgg cag tca ata cca ctc tgt       2592
Glu Glu Ile Thr Cys Lys Asp Gly Arg Trp Gln Ser Ile Pro Leu Cys
    850                 855                 860

gtt gaa aaa att cca tgt tca caa cca cct cag ata gaa cac gga acc       2640
Val Glu Lys Ile Pro Cys Ser Gln Pro Pro Gln Ile Glu His Gly Thr
```

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865                 870                 875                 880

att aat tca tcc agg tct tca caa gaa agt tat gca cat ggg act aaa       2688
Ile Asn Ser Ser Arg Ser Ser Gln Glu Ser Tyr Ala His Gly Thr Lys
                885                 890                 895

ttg agt tat act tgt gag ggt ggt ttc agg ata tct gaa gaa aat gaa       2736
Leu Ser Tyr Thr Cys Glu Gly Gly Phe Arg Ile Ser Glu Glu Asn Glu
            900                 905                 910

aca aca tgc tac atg gga aaa tgg agt tct cca cct cag tgt gaa ggc       2784
Thr Thr Cys Tyr Met Gly Lys Trp Ser Ser Pro Pro Gln Cys Glu Gly
        915                 920                 925

ctt cct tgt aaa tct cca cct gag att tct cat ggt gtt gta gct cac       2832
Leu Pro Cys Lys Ser Pro Pro Glu Ile Ser His Gly Val Val Ala His
    930                 935                 940

atg tca gac agt tat cag tat gga gaa gaa gtt acg tac aaa tgt ttt       2880
Met Ser Asp Ser Tyr Gln Tyr Gly Glu Glu Val Thr Tyr Lys Cys Phe
945                 950                 955                 960

gaa ggt ttt gga att gat ggg cct gca att gca aaa tgc tta gga gaa       2928
Glu Gly Phe Gly Ile Asp Gly Pro Ala Ile Ala Lys Cys Leu Gly Glu
                965                 970                 975

aaa tgg tct cac cct cca tca tgc ata aaa aca gat tgt ctc agt tta       2976
Lys Trp Ser His Pro Pro Ser Cys Ile Lys Thr Asp Cys Leu Ser Leu
            980                 985                 990

cct agc ttt gaa aat gcc ata ccc  atg gga gag aag aag  gat gtg tat     3024
Pro Ser Phe Glu Asn Ala Ile Pro  Met Gly Glu Lys Lys  Asp Val Tyr
        995                 1000                1005

aag gcg  ggt gag caa gtg act  tac act tgt gca aca  tat tac aaa       3069
Lys Ala  Gly Glu Gln Val Thr  Tyr Thr Cys Ala Thr  Tyr Tyr Lys
    1010                1015                1020

atg gat  gga gcc agt aat gta  aca tgc att aat agc  aga tgg aca       3114
Met Asp  Gly Ala Ser Asn Val  Thr Cys Ile Asn Ser  Arg Trp Thr
    1025                1030                1035

gga agg  cca aca tgc aga gac  acc tcc tgt gtg aat  ccg ccc aca       3159
Gly Arg  Pro Thr Cys Arg Asp  Thr Ser Cys Val Asn  Pro Pro Thr
    1040                1045                1050

gta caa  aat gct tat ata gtg  tcg aga cag atg agt  aaa tat cca       3204
Val Gln  Asn Ala Tyr Ile Val  Ser Arg Gln Met Ser  Lys Tyr Pro
    1055                1060                1065

tct ggt  gag aga gta cgt tat  caa tgt agg agc cct  tat gaa atg       3249
Ser Gly  Glu Arg Val Arg Tyr  Gln Cys Arg Ser Pro  Tyr Glu Met
    1070                1075                1080

ttt ggg  gat gaa gaa gtg atg  tgt tta aat gga aac  tgg acg gaa       3294
Phe Gly  Asp Glu Glu Val Met  Cys Leu Asn Gly Asn  Trp Thr Glu
    1085                1090                1095

cca cct  caa tgc aaa gat tct  aca gga aaa tgt ggg  ccc cct cca       3339
Pro Pro  Gln Cys Lys Asp Ser  Thr Gly Lys Cys Gly  Pro Pro Pro
    1100                1105                1110

cct att  gac aat ggg gac att  act tca ttc ccg ttg  tca gta tat       3384
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Pro Ile  Asp Asn Gly Asp Ile  Thr Ser Phe Pro Leu  Ser Val Tyr
    1115                1120                1125

gct cca  gct tca tca gtt gag  tac caa tgc cag aac  ttg tat caa        3429
Ala Pro  Ala Ser Ser Val Glu  Tyr Gln Cys Gln Asn  Leu Tyr Gln
    1130                1135                1140

ctt gag  ggt aac aag cga ata  aca tgt aga aat gga  caa tgg tca        3474
Leu Glu  Gly Asn Lys Arg Ile  Thr Cys Arg Asn Gly  Gln Trp Ser
    1145                1150                1155

gaa cca  cca aaa tgc tta cat  ccg tgt gta ata tcc  cga gaa att        3519
Glu Pro  Pro Lys Cys Leu His  Pro Cys Val Ile Ser  Arg Glu Ile
    1160                1165                1170

atg gaa  aat tat aac ata gca  tta agg tgg aca gcc  aaa cag aag        3564
Met Glu  Asn Tyr Asn Ile Ala  Leu Arg Trp Thr Ala  Lys Gln Lys
    1175                1180                1185

ctt tat  tcg aga aca ggt gaa  tca gtt gaa ttt gtg  tgt aaa cgg        3609
Leu Tyr  Ser Arg Thr Gly Glu  Ser Val Glu Phe Val  Cys Lys Arg
    1190                1195                1200

gga tat  cgt ctt tca tca cgt  tct cac aca ttg cga  aca aca tgt        3654
Gly Tyr  Arg Leu Ser Ser Arg  Ser His Thr Leu Arg  Thr Thr Cys
    1205                1210                1215

tgg gat  ggg aaa ctg gag tat  cca act tgt gca aaa  aga tag            3696
Trp Asp  Gly Lys Leu Glu Tyr  Pro Thr Cys Ala Lys  Arg
    1220                1225                1230
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<400> 2

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Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1               5                   10                  15

Val Ala
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<210> 3
<211> 62
<212> PRT
<213> Homo sapiens

<400> 3

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Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile Leu Thr
1               5                   10                  15

Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala Ile Tyr
            20                  25                  30

Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Ile Ile Met Val Cys
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35 40 45

Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys
50 55 60

<210> 4
<211> 4
<212> PRT
<213> Homo sapiens

<400> 4

Gln Lys Arg Pro
1

<210> 5
<211> 57
<212> PRT
<213> Homo sapiens

<400> 5

Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe Thr Leu Thr Gly
1 5 10 15

Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr Thr Cys Asn Glu
20 25 30

Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu Cys Asp Thr Asp
35 40 45

Gly Trp Thr Asn Asp Ile Pro Ile Cys
50 55

<210> 6
<211> 4
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<213> Homo sapiens

<400> 6

Glu Val Val Lys
1

<210> 7
<211> 60
<212> PRT
<213> Homo sapiens

<400> 7

Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser Ala
1 5 10 15

Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe Val
20 25 30

Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys Ser
35 40 45

Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys
50 55 60

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Val Glu Ile Ser
1

<210> 9
<211> 53
<212> PRT
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<400> 9

Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys Ile
1 5 10 15

Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly Tyr
20 25 30

Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp Arg
35 40 45

Pro Leu Pro Ser Cys
50

<210> 10
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<212> PRT
<213> Homo sapiens

<400> 10

Glu Glu Lys Ser
1

<210> 11
<211> 54
<212> PRT
<213> Homo sapiens

<400> 11

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Cys Asp Asn Pro Tyr Ile Pro Asn Gly Asp Tyr Ser Pro Leu Arg Ile
1               5                   10                  15

Lys His Arg Thr Gly Asp Glu Ile Thr Tyr Gln Cys Arg Asn Gly Phe
            20                  25                  30

Tyr Pro Ala Thr Arg Gly Asn Thr Ala Lys Cys Thr Ser Thr Gly Trp
        35                  40                  45

Ile Pro Ala Pro Arg Cys
    50
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<400> 12

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Thr Leu Lys Pro
1
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<210> 13
<211> 61
<212> PRT
<213> Homo sapiens

<400> 13

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Cys Asp Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr His Glu Asn Met
1               5                   10                  15

Arg Arg Pro Tyr Phe Pro Val Ala Val Gly Lys Tyr Tyr Ser Tyr Tyr
            20                  25                  30

Cys Asp Glu His Phe Glu Thr Pro Ser Gly Ser Tyr Trp Asp His Ile
        35                  40                  45

His Cys Thr Gln Asp Gly Trp Ser Pro Ala Val Pro Cys
    50                  55                  60
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<210> 14
<211> 54
<212> PRT
<213> Homo sapiens

<400> 14

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Cys Tyr Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln Asn Tyr Gly Arg
1               5                   10                  15

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

Ala Leu Pro Lys Ala Gln Thr Thr Val Thr Cys Met Glu Asn Gly Trp
35 40 45

Ser Pro Thr Pro Arg Cys
50

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Ile Arg Val Lys Thr
1 5

<210> 16
<211> 58
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<400> 16

Cys Ser Lys Ser Ser Ile Asp Ile Glu Asn Gly Phe Ile Ser Glu Ser
1 5 10 15

Gln Tyr Thr Tyr Ala Leu Lys Glu Lys Ala Lys Tyr Gln Cys Lys Leu
20 25 30

Gly Tyr Val Thr Ala Asp Gly Glu Thr Ser Gly Ser Ile Thr Cys Gly
35 40 45

Lys Asp Gly Trp Ser Ala Gln Pro Thr Cys
50 55

<210> 17
<211> 56
<212> PRT
<213> Homo sapiens

<400> 17

Cys Asp Ile Pro Val Phe Met Asn Ala Arg Thr Lys Asn Asp Phe Thr
1 5 10 15

Trp Phe Lys Leu Asn Asp Thr Leu Asp Tyr Glu Cys His Asp Gly Tyr
20 25 30

Glu Ser Asn Thr Gly Ser Thr Thr Gly Ser Ile Val Cys Gly Tyr Asn
35 40 45

Gly Trp Ser Asp Leu Pro Ile Cys
    50   55

<210> 18
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Tyr Glu Arg Glu
1

<210> 19
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<400> 19

Cys Glu Leu Pro Lys Ile Asp Val His Leu Val Pro Asp Arg Lys Lys
1   5   10   15

Asp Gln Tyr Lys Val Gly Glu Val Leu Lys Phe Ser Cys Lys Pro Gly
            20   25   30

Phe Thr Ile Val Gly Pro Asn Ser Val Gln Cys Tyr His Phe Gly Leu
        35   40   45

Ser Pro Asp Leu Pro Ile Cys
    50   55

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Lys Glu Gln Val Gln Ser
1   5

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<400> 21

Cys Gly Pro Pro Pro Glu Leu Leu Asn Gly Asn Val Lys Glu Lys Thr
1   5   10   15

Lys Glu Glu Tyr Gly His Ser Glu Val Val Glu Tyr Tyr Cys Asn Pro
            20   25   30

Arg Phe Leu Met Lys Gly Pro Asn Lys Ile Gln Cys Val Asp Gly Glu
35 40 45

Trp Thr Thr Leu Pro Val Cys
50 55

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<400> 22

Ile Val Glu Glu Ser Thr
1 5

<210> 23
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<400> 23

Cys Gly Asp Ile Pro Glu Leu Glu His Gly Trp Ala Gln Leu Ser Ser
1 5 10 15

Pro Pro Tyr Tyr Tyr Gly Asp Ser Val Glu Phe Asn Cys Ser Glu Ser
20 25 30

Phe Thr Met Ile Gly His Arg Ser Ile Thr Cys Ile His Gly Val Trp
35 40 45

Thr Gln Leu Pro Gln Cys
50

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Val Ala Ile Asp Lys Leu Lys Lys
1 5

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Cys Lys Ser Ser Asn Leu Ile Ile Leu Glu Glu His Leu Lys Asn Lys

1 5 10 15

Lys Glu Phe Asp His Asn Ser Asn Ile Arg Tyr Arg Cys Arg Gly Lys
20 25 30

Glu Gly Trp Ile His Thr Val Cys Ile Asn Gly Arg Trp Asp Pro Glu
35 40 45

Val Asn Cys
50

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Ser Met Ala Gln Ile Gln Leu
1 5

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Cys Pro Pro Pro Pro Gln Ile Pro Asn Ser His Asn Met Thr Thr Thr
1 5 10 15

Leu Asn Tyr Arg Asp Gly Glu Lys Val Ser Val Leu Cys Gln Glu Asn
20 25 30

Tyr Leu Ile Gln Glu Gly Glu Glu Ile Thr Cys Lys Asp Gly Arg Trp
35 40 45

Gln Ser Ile Pro Leu Cys
50

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Val Glu Lys Ile Pro
1 5

<210> 29
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Cys Ser Gln Pro Pro Gln Ile Glu His Gly Thr Ile Asn Ser Ser Arg
1 5 10 15

Ser Ser Gln Glu Ser Tyr Ala His Gly Thr Lys Leu Ser Tyr Thr Cys
20 25 30

Glu Gly Gly Phe Arg Ile Ser Glu Glu Asn Glu Thr Thr Cys Tyr Met
35 40 45

Gly Lys Trp Ser Ser Pro Pro Gln Cys
50 55

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Glu Gly Leu Pro
1

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Cys Lys Ser Pro Pro Glu Ile Ser His Gly Val Val Ala His Met Ser
1 5 10 15

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

Phe Gly Ile Asp Gly Pro Ala Ile Ala Lys Cys Leu Gly Glu Lys Trp
35 40 45

Ser His Pro Pro Ser Cys
50

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Ile Lys Thr Asp
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Cys Leu Ser Leu Pro Ser Phe Glu Asn Ala Ile Pro Met Gly Glu Lys
1 5 10 15

Lys Asp Val Tyr Lys Ala Gly Glu Gln Val Thr Tyr Thr Cys Ala Thr
20 25 30

Tyr Tyr Lys Met Asp Gly Ala Ser Asn Val Thr Cys Ile Asn Ser Arg
35 40 45

Trp Thr Gly Arg Pro Thr Cys
50 55

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Arg Asp Thr Ser
1

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Cys Val Asn Pro Pro Thr Val Gln Asn Ala Tyr Ile Val Ser Arg Gln
1 5 10 15

Met Ser Lys Tyr Pro Ser Gly Glu Arg Val Arg Tyr Gln Cys Arg Ser
20 25 30

Pro Tyr Glu Met Phe Gly Asp Glu Glu Val Met Cys Leu Asn Gly Asn
35 40 45

Trp Thr Glu Pro Pro Gln Cys
50 55

<210> 36
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Lys Asp Ser Thr Gly Lys
1 5

<210> 37
<211> 55
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Cys Gly Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile Thr Ser Phe Pro
1 5 10 15

Leu Ser Val Tyr Ala Pro Ala Ser Ser Val Glu Tyr Gln Cys Gln Asn
20 25 30

Leu Tyr Gln Leu Glu Gly Asn Lys Arg Ile Thr Cys Arg Asn Gly Gln
35 40 45

Trp Ser Glu Pro Pro Lys Cys
50 55

<210> 38
<211> 65
<212> PRT
<213> Homo sapiens

<400> 38

Cys Val Ile Ser Arg Glu Ile Met Glu Asn Tyr Asn Ile Ala Leu Arg
1 5 10 15

Trp Thr Ala Lys Gln Lys Leu Tyr Ser Arg Thr Gly Glu Ser Val Glu
20 25 30

Phe Val Cys Lys Arg Gly Tyr Arg Leu Ser Ser Arg Ser His Thr Leu
35 40 45

Arg Thr Thr Cys Trp Asp Gly Lys Leu Glu Tyr Pro Thr Cys Ala Lys
50 55 60

Arg
65

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<222> (868)..(928)
<223> Sushi 15

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<222> (929)..(986)
<223> Sushi 16

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<222> (987)..(1045)
<223> Sushi 17

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<222> (1046)..(1104)
<223> Sushi 18

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<222> (1107)..(1165)
<223> Sushi 19

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<222> (1170)..(1230)
<223> Sushi 20

<400> 39

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Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1               5                  10                  15


Val Ala Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile
            20                  25                  30


Leu Thr Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala
        35                  40                  45


Ile Tyr Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Val Ile Met
    50                  55                  60


Val Cys Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys
65                  70                  75                  80
```

```
Gln Lys Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe
                85                  90                  95

Thr Leu Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr
            100                 105                 110

Thr Cys Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu
        115                 120                 125

Cys Asp Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val
    130                 135                 140

Lys Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser
145                 150                 155                 160

Ala Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe
                165                 170                 175

Val Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys
            180                 185                 190

Ser Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile
        195                 200                 205

Ser Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys
    210                 215                 220

Ile Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly
225                 230                 235                 240

Tyr Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp
                245                 250                 255

Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Cys Asp Asn Pro Tyr Ile
            260                 265                 270

Pro Asn Gly Asp Tyr Ser Pro Leu Arg Ile Lys His Arg Thr Gly Asp
        275                 280                 285

Glu Ile Thr Tyr Gln Cys Arg Asn Gly Phe Tyr Pro Ala Thr Arg Gly
    290                 295                 300

Asn Thr Ala Lys Cys Thr Ser Thr Gly Trp Ile Pro Ala Pro Arg Cys
305                 310                 315                 320

Thr Leu Lys Pro Cys Asp Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr
                325                 330                 335
```

```
His Glu Asn Met Arg Arg Pro Tyr Phe Pro Val Ala Val Gly Lys Tyr
            340                 345                 350

Tyr Ser Tyr Tyr Cys Asp Glu His Phe Glu Thr Pro Ser Gly Ser Tyr
        355                 360                 365

Trp Asp His Ile His Cys Thr Gln Asp Gly Trp Ser Pro Ala Val Pro
    370                 375                 380

Cys Leu Arg Lys Cys Tyr Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln
385                 390                 395                 400

Asn Tyr Gly Arg Lys Phe Val Gln Gly Lys Ser Ile Asp Val Ala Cys
                405                 410                 415

His Pro Gly Tyr Ala Leu Pro Lys Ala Gln Thr Thr Val Thr Cys Met
            420                 425                 430

Glu Asn Gly Trp Ser Pro Thr Pro Arg Cys Ile Arg Val Lys Thr Cys
        435                 440                 445

Ser Lys Ser Ser Ile Asp Ile Glu Asn Gly Phe Ile Ser Glu Ser Gln
    450                 455                 460

Tyr Thr Tyr Ala Leu Lys Glu Lys Ala Lys Tyr Gln Cys Lys Leu Gly
465                 470                 475                 480

Tyr Val Thr Ala Asp Gly Glu Thr Ser Gly Ser Ile Thr Cys Gly Lys
                485                 490                 495

Asp Gly Trp Ser Ala Gln Pro Thr Cys Ile Lys Ser Cys Asp Ile Pro
            500                 505                 510

Val Phe Met Asn Ala Arg Thr Lys Asn Asp Phe Thr Trp Phe Lys Leu
        515                 520                 525

Asn Asp Thr Leu Asp Tyr Glu Cys His Asp Gly Tyr Glu Ser Asn Thr
    530                 535                 540

Gly Ser Thr Thr Gly Ser Ile Val Cys Gly Tyr Asn Gly Trp Ser Asp
545                 550                 555                 560

Leu Pro Ile Cys Tyr Glu Arg Glu Cys Glu Leu Pro Lys Ile Asp Val
                565                 570                 575

His Leu Val Pro Asp Arg Lys Lys Asp Gln Tyr Lys Val Gly Glu Val
            580                 585                 590
```

```
Leu Lys Phe Ser Cys Lys Pro Gly Phe Thr Ile Val Gly Pro Asn Ser
        595                 600                 605

Val Gln Cys Tyr His Phe Gly Leu Ser Pro Asp Leu Pro Ile Cys Lys
    610                 615                 620

Glu Gln Val Gln Ser Cys Gly Pro Pro Pro Glu Leu Leu Asn Gly Asn
625                 630                 635                 640

Val Lys Glu Lys Thr Lys Glu Glu Tyr Gly His Ser Glu Val Val Glu
                645                 650                 655

Tyr Tyr Cys Asn Pro Arg Phe Leu Met Lys Gly Pro Asn Lys Ile Gln
            660                 665                 670

Cys Val Asp Gly Glu Trp Thr Thr Leu Pro Val Cys Ile Val Glu Glu
        675                 680                 685

Ser Thr Cys Gly Asp Ile Pro Glu Leu Glu His Gly Trp Ala Gln Leu
    690                 695                 700

Ser Ser Pro Pro Tyr Tyr Tyr Gly Asp Ser Val Glu Phe Asn Cys Ser
705                 710                 715                 720

Glu Ser Phe Thr Met Ile Gly His Arg Ser Ile Thr Cys Ile His Gly
                725                 730                 735

Val Trp Thr Gln Leu Pro Gln Cys Val Ala Ile Asp Lys Leu Lys Lys
            740                 745                 750

Cys Lys Ser Ser Asn Leu Ile Ile Leu Glu Glu His Leu Lys Asn Lys
        755                 760                 765

Lys Glu Phe Asp His Asn Ser Asn Ile Arg Tyr Arg Cys Arg Gly Lys
    770                 775                 780

Glu Gly Trp Ile His Thr Val Cys Ile Asn Gly Arg Trp Asp Pro Glu
785                 790                 795                 800

Val Asn Cys Ser Met Ala Gln Ile Gln Leu Cys Pro Pro Pro Pro Gln
                805                 810                 815

Ile Pro Asn Ser His Asn Met Thr Thr Thr Leu Asn Tyr Arg Asp Gly
            820                 825                 830

Glu Lys Val Ser Val Leu Cys Gln Glu Asn Tyr Leu Ile Gln Glu Gly
```

835 840 845

Glu Glu Ile Thr Cys Lys Asp Gly Arg Trp Gln Ser Ile Pro Leu Cys
850 855 860

Val Glu Lys Ile Pro Cys Ser Gln Pro Pro Gln Ile Glu His Gly Thr
865 870 875 880

Ile Asn Ser Ser Arg Ser Ser Gln Glu Ser Tyr Ala His Gly Thr Lys
885 890 895

Leu Ser Tyr Thr Cys Glu Gly Gly Phe Arg Ile Ser Glu Glu Asn Glu
900 905 910

Thr Thr Cys Tyr Met Gly Lys Trp Ser Ser Pro Pro Gln Cys Glu Gly
915 920 925

Leu Pro Cys Lys Ser Pro Pro Glu Ile Ser His Gly Val Val Ala His
930 935 940

Met Ser Asp Ser Tyr Gln Tyr Gly Glu Glu Val Thr Tyr Lys Cys Phe
945 950 955 960

Glu Gly Phe Gly Ile Asp Gly Pro Ala Ile Ala Lys Cys Leu Gly Glu
965 970 975

Lys Trp Ser His Pro Pro Ser Cys Ile Lys Thr Asp Cys Leu Ser Leu
980 985 990

Pro Ser Phe Glu Asn Ala Ile Pro Met Gly Glu Lys Lys Asp Val Tyr
995 1000 1005

Lys Ala Gly Glu Gln Val Thr Tyr Thr Cys Ala Thr Tyr Tyr Lys
1010 1015 1020

Met Asp Gly Ala Ser Asn Val Thr Cys Ile Asn Ser Arg Trp Thr
1025 1030 1035

Gly Arg Pro Thr Cys Arg Asp Thr Ser Cys Val Asn Pro Pro Thr
1040 1045 1050

Val Gln Asn Ala Tyr Ile Val Ser Arg Gln Met Ser Lys Tyr Pro
1055 1060 1065

Ser Gly Glu Arg Val Arg Tyr Gln Cys Arg Ser Pro Tyr Glu Met
1070 1075 1080

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Phe Gly  Asp Glu Glu Val Met  Cys Leu Asn Gly Asn  Trp Thr Glu
    1085                1090                1095

Pro Pro  Gln Cys Lys Asp Ser  Thr Gly Lys Cys Gly  Pro Pro Pro
    1100                1105                1110

Pro Ile  Asp Asn Gly Asp Ile  Thr Ser Phe Pro Leu  Ser Val Tyr
    1115                1120                1125

Ala Pro  Ala Ser Ser Val Glu  Tyr Gln Cys Gln Asn  Leu Tyr Gln
    1130                1135                1140

Leu Glu  Gly Asn Lys Arg Ile  Thr Cys Arg Asn Gly  Gln Trp Ser
    1145                1150                1155

Glu Pro  Pro Lys Cys Leu His  Pro Cys Val Ile Ser  Arg Glu Ile
    1160                1165                1170

Met Glu  Asn Tyr Asn Ile Ala  Leu Arg Trp Thr Ala  Lys Gln Lys
    1175                1180                1185

Leu Tyr  Ser Arg Thr Gly Glu  Ser Val Glu Phe Val  Cys Lys Arg
    1190                1195                1200

Gly Tyr  Arg Leu Ser Ser Arg  Ser His Thr Leu Arg  Thr Thr Cys
    1205                1210                1215

Trp Asp  Gly Lys Leu Glu Tyr  Pro Thr Cys Ala Lys  Arg
    1220                1225                1230


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<212>  PRT
<213>  Homo sapiens

<400>  40

Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1               5                  10                  15

Val Ala Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile
            20                  25                  30

Leu Thr Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala
        35                  40                  45

Ile Tyr Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Val Ile Met
    50                  55                  60
```

```
Val Cys Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys
65                  70                  75                  80

Gln Lys Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe
                85                  90                  95

Thr Leu Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr
            100                 105                 110

Thr Cys Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu
        115                 120                 125

Cys Asp Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val
    130                 135                 140

Lys Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser
145                 150                 155                 160

Ala Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe
                165                 170                 175

Val Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys
            180                 185                 190

Ser Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile
        195                 200                 205

Ser Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys
    210                 215                 220

Ile Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly
225                 230                 235                 240

Tyr Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp
                245                 250                 255

Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Cys Asp Asn Pro Tyr Ile
            260                 265                 270

Pro Asn Gly Asp Tyr Ser Pro Leu Arg Ile Lys His Arg Thr Gly Asp
        275                 280                 285

Glu Ile Thr Tyr Gln Cys Arg Asn Gly Phe Tyr Pro Ala Thr Arg Gly
    290                 295                 300

Asn Thr Ala Lys Cys Thr Ser Thr Gly Trp Ile Pro Ala Pro Arg Cys
305                 310                 315                 320
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Thr Leu Lys Pro Cys Asp Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr
325 330 335

His Glu Asn Met Arg Arg Pro Tyr Phe Pro Val Ala Val Gly Lys Tyr
340 345 350

Tyr Ser Tyr Tyr Cys Asp Glu His Phe Glu Thr Pro Ser Gly Ser Tyr
355 360 365

Trp Asp His Ile His Cys Thr Gln Asp Gly Trp Ser Pro Ala Val Pro
370 375 380

Cys Leu Arg Lys Cys Tyr Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln
385 390 395 400

Asn Tyr Gly Arg Lys Phe Val Gln Gly Lys Ser Ile Asp Val Ala Cys
405 410 415

His Pro Gly Tyr Ala Leu Pro Lys Ala Gln Thr Thr Val Thr Cys Met
420 425 430

Glu Asn Gly Trp Ser Pro Thr Pro Arg Cys Ile Arg Val Ser Phe Thr
435 440 445

Leu

<210> 41
<211> 2068
<212> DNA
<213> Artificial sequence

<220>
<223> engineered hfH1-4.678.19-20 variant cDNA

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acttcctcca agaagaaata cagaaattct gacaggttcc tggtctgacc aaacatatcc 180

agaaggcacc caggctatct ataaatgccg ccctggatat agatctcttg gaaatataat 240

aatggtatgc aggaagggag aatgggttgc tcttaatcca ttaaggaaat gtcagaaaag 300

gccctgtgga catcctggag atactccttt tggtactttt acccttacag gaggaaatgt 360

gtttgaatat ggtgtaaaag ctgtgtatac atgtaatgag gggtatcaat tgctaggtga 420

gattaattac cgtgaatgtg acacagatgg atggaccaat gatattccta tatgtgaagt 480

tgtgaagtgt ttaccagtga cagcaccaga gaatggaaaa attgtcagta gtgcaatgga 540

accagatcgg gaataccatt ttggacaagc agtacggttt gtatgtaact caggctacaa 600

gattgaagga gatgaagaaa tgcattgttc agacgatggt ttttggagta aagagaaacc 660

aaagtgtgtg gaaatttcat gcaaatcccc agatgttata aatggatctc ctatatctca 720

gaagattatt tataaggaga atgaacgatt tcaatataaa tgtaacatgg gttatgaata 780

cagtgaaaga ggagatgctg tatgcactga atctggatgg cgtccgttgc cttcatgtga 840

agaaaaatca accttgaaac cttgtgatta tccagacatt aaacatggag gtctatatca 900

tgagaatatg cgtagaccat actttccagt agctgtagga aaatattact cctattactg 960

tgatgaacat tttgagactc cgtcaggaag ttactgggat cacattcatt gcacacaaga 1020

tggatggtcg ccagcagtac catgcctcag aaaatgttat tttccttatt tggaaaatgg 1080

atataatcaa aatcatggaa gaaagtttgt acagggtaaa tctatagacg ttgcctgcca 1140

tcctggctac gctcttccaa aagcgcagac cacagttaca tgtatggaga atggctggtc 1200

tcctactccc agatgcatcc gtgtcaaaac atgttccaaa tcaagtatag atattgagaa 1260

tgggtttatt tctgaatctc agtatacata tgccttaaaa gaaaaagcga aatatcaatg 1320

caaactagga tatgtaacag cagatggtga aacatcagga tcaattagat gtgggaaaga 1380

tggatggtca gctcaaccca cgtgcattaa atctaaagat tctacaggaa aatgtgggcc 1440

ccctccacct attgacaatg gggacattac ttcattcccg ttgtcagtat atgctccagc 1500

ttcatcagtt gagtaccaat gccagaactt gtatcaactt gagggtaaca agcgaataac 1560

atgtagaaat ggacaatggt cagaaccacc aaaatgctta catccgtgtg taatatcccg 1620

agaaattatg gaaaattata acatagcatt aaggtggaca gccaaacaga agctttattc 1680

gagaacaggt gaatcagttg aatttgtgtg taaacgggga tatcgtcttt catcacgttc 1740

tcacacattg cgaacaacat gttgggatgg gaaactggag tatccaactt gtgcaaaaag 1800

atagaatcaa tcataaagtg cacaccttta ttcagaactt tagtattaaa tcagttctca 1860

atttcatttt ttatgtattg ttttactcct ttttattcat acgtaaaatt ttggattaat 1920

ttgtgaaaat gtaattataa gctgagaccg gtggctctct tcttaaaagc accatattaa 1980

atcctggaaa actaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2040

aaaaaaaaaa aaaaaaaaaa aaaaaaaa 2068

<210> 42
<211> 583
<212> PRT
<213> Artificial sequence

<220>
<223> hfH1-4.678.19-20 protein

<400> 42

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Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1               5                  10                  15

Val Ala Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile
            20                  25                  30

Leu Thr Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala
        35                  40                  45

Ile Tyr Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Val Ile Met
    50                  55                  60

Val Cys Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys
65                  70                  75                  80

Gln Lys Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe
                85                  90                  95

Thr Leu Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr
            100                 105                 110

Thr Cys Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu
        115                 120                 125

Cys Asp Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val
    130                 135                 140

Lys Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser
145                 150                 155                 160

Ala Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe
                165                 170                 175

Val Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys
            180                 185                 190

Ser Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile
        195                 200                 205

Ser Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys
    210                 215                 220

Ile Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly
225                 230                 235                 240

Tyr Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp
                245                 250                 255
```

```
Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Thr Leu Lys Pro Cys Asp
            260                 265                 270

Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr His Glu Asn Met Arg Arg
        275                 280                 285

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

Glu His Phe Glu Thr Pro Ser Gly Ser Tyr Trp Asp His Ile His Cys
305                 310                 315                 320

Thr Gln Asp Gly Trp Ser Pro Ala Val Pro Cys Leu Arg Lys Cys Tyr
                325                 330                 335

Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln Asn His Gly Arg Lys Phe
            340                 345                 350

Val Gln Gly Lys Ser Ile Asp Val Ala Cys His Pro Gly Tyr Ala Leu
        355                 360                 365

Pro Lys Ala Gln Thr Thr Val Thr Cys Met Glu Asn Gly Trp Ser Pro
    370                 375                 380

Thr Pro Arg Cys Ile Arg Val Lys Thr Cys Ser Lys Ser Ser Ile Asp
385                 390                 395                 400

Ile Glu Asn Gly Phe Ile Ser Glu Ser Gln Tyr Thr Tyr Ala Leu Lys
                405                 410                 415

Glu Lys Ala Lys Tyr Gln Cys Lys Leu Gly Tyr Val Thr Ala Asp Gly
            420                 425                 430

Glu Thr Ser Gly Ser Ile Arg Cys Gly Lys Asp Gly Trp Ser Ala Gln
        435                 440                 445

Pro Thr Cys Ile Lys Ser Lys Asp Ser Thr Gly Lys Cys Gly Pro Pro
    450                 455                 460

Pro Pro Ile Asp Asn Gly Asp Ile Thr Ser Phe Pro Leu Ser Val Tyr
465                 470                 475                 480

Ala Pro Ala Ser Ser Val Glu Tyr Gln Cys Gln Asn Leu Tyr Gln Leu
                485                 490                 495

Glu Gly Asn Lys Arg Ile Thr Cys Arg Asn Gly Gln Trp Ser Glu Pro
```

500 505 510

Pro Lys Cys Leu His Pro Cys Val Ile Ser Arg Glu Ile Met Glu Asn
515 520 525

Tyr Asn Ile Ala Leu Arg Trp Thr Ala Lys Gln Lys Leu Tyr Ser Arg
530 535 540

Thr Gly Glu Ser Val Glu Phe Val Cys Lys Arg Gly Tyr Arg Leu Ser
545 550 555 560

Ser Arg Ser His Thr Leu Arg Thr Thr Cys Trp Asp Gly Lys Leu Glu
565 570 575

Tyr Pro Thr Cys Ala Lys Arg
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<210> 43
<211> 2406
<212> DNA
<213> Artificial sequence

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<400> 43
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atccaaatta tgagactgtc agcaagaatt atttggctta tattatggac tgtttgtgca 240

gcagaagatt gtaaaggtcc tcctccaaga gaaaattcag aaattctctc aggctcgtgg 300

tcagaacaac tatatccaga aggcacccag gctacctaca aatgccgccc tggataccga 360

acacttggca ctattgtaaa agtatgcaag aatggaaaat gggtggcgtc taacccatcc 420

aggatatgtc ggaaaaagcc ttgtgggcat cccggagaca cacccttgg gtcctttagg 480

ctggcagttg gatctcaatt tgagtttggt gcaaaggttg tttatacctg tgatgatggg 540

tatcaactat taggtgaaat tgattaccgt gaatgtggtg cagatgggtg gatcaatgat 600

attccactat gtgaagttgt gaagtgtcta cctgtgacag aactcgagaa tggaagaatt 660

gtgagtggtg cagcagaaac agaccaggaa tactattttg gacaggtggt gcggtttgaa 720

tgcaattcag gcttcaagat tgaaggacat aaggaaattc attgctcaga aaatggcctt 780

tggagcaatg aaaagccacg atgtgtggaa attctctgca caccaccgcg agtggaaaat 840

ggagatggta taaatgtgaa accagtttac aaggagaatg aaagatacca ctataagtgt 900

aagcatggtt atgtgcccaa agaaagaggg gatgccgtct gcacaggctc tggatggagt 960

tctcagcctt tctgtgaaga aaagagaacc ttgaaaccat gtgaatttcc acaattcaaa 1020

tatggacgtc tgtattatga agagagcctg agacccaact tcccagtatc tataggaaat 1080

aagtacagct ataagtgtga caacgggttt tcaccacctt ctgggtattc ctgggactac 1140

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cattatgtgg agaatggaga ctctgcatac tgggaaaaag tatatgtgca gggtcagtct 1260

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acagagaatg gctggtcccc tcctcccaaa tgcatccgta tcaagacatg ttcagcatca 1380

gatatacaca ttgacaatgg atttctttct gaatcttctt ctatatatgc tctaaataga 1440

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acagggaaat gtgggcctcc tccacctatt gacaatggag acatcacctc cttgtcatta 1620

ccagtatatg aaccattatc atcagttgaa tatcaatgcc agaagtatta tctccttaag 1680

ggaaagaaga caataacatg tagaaatgga aagtggtctg agccaccaac atgcttacat 1740

gcatgtgtaa taccagaaaa cattatggaa tcacacaata taattctcaa atggagacac 1800

actgaaaaga tttattccca ttcaggggag gatattgaat ttggatgtaa atatggatat 1860

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atgcatgtga ctaatatact ttcaatttgc attgaagtat tgtttaactc atgtcttctc 2040

ataaatataa acatttttgt tatatggtga ttaatttgta actttaaaaa ctattgccaa 2100

aatgcaaaag cagtaattca aaactcctaa tctaaaatat gatatgtcca aggacaaact 2160

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gactgattct tcaaattaat atgatttccc aaagcatgta acaaccaaac tatcatatat 2340

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<210> 44
<211> 599
<212> PRT
<213> Artificial sequence

<220>
<223> mouse factor H truncation construct mFH1-4.678.19-20

<400> 44

Met Val Gln His Arg Phe Leu Leu Glu Ser Val Gly Pro Arg Lys Ile

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Gln Ile Met Arg Leu Ser Ala Arg Ile Ile Trp Leu Ile Leu Trp Thr
            20                  25                  30

Val Cys Ala Ala Glu Asp Cys Lys Gly Pro Pro Pro Arg Glu Asn Ser
        35                  40                  45

Glu Ile Leu Ser Gly Ser Trp Ser Glu Gln Leu Tyr Pro Glu Gly Thr
    50                  55                  60

Gln Ala Thr Tyr Lys Cys Arg Pro Gly Tyr Arg Thr Leu Gly Thr Ile
65                  70                  75                  80

Val Lys Val Cys Lys Asn Gly Lys Trp Val Ala Ser Asn Pro Ser Arg
                85                  90                  95

Ile Cys Arg Lys Lys Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly
            100                 105                 110

Ser Phe Arg Leu Ala Val Gly Ser Gln Phe Glu Phe Gly Ala Lys Val
        115                 120                 125

Val Tyr Thr Cys Asp Asp Gly Tyr Gln Leu Leu Gly Glu Ile Asp Tyr
    130                 135                 140

Arg Glu Cys Gly Ala Asp Gly Trp Ile Asn Asp Ile Pro Leu Cys Glu
145                 150                 155                 160

Val Val Lys Cys Leu Pro Val Thr Glu Leu Glu Asn Gly Arg Ile Val
                165                 170                 175

Ser Gly Ala Ala Glu Thr Asp Gln Glu Tyr Tyr Phe Gly Gln Val Val
            180                 185                 190

Arg Phe Glu Cys Asn Ser Gly Phe Lys Ile Glu Gly His Lys Glu Ile
        195                 200                 205

His Cys Ser Glu Asn Gly Leu Trp Ser Asn Glu Lys Pro Arg Cys Val
    210                 215                 220

Glu Ile Leu Cys Thr Pro Pro Arg Val Glu Asn Gly Asp Gly Ile Asn
225                 230                 235                 240

Val Lys Pro Val Tyr Lys Glu Asn Glu Arg Tyr His Tyr Lys Cys Lys
                245                 250                 255
```

```
His Gly Tyr Val Pro Lys Glu Arg Gly Asp Ala Val Cys Thr Gly Ser
            260                 265                 270

Gly Trp Ser Ser Gln Pro Phe Cys Glu Glu Lys Arg Thr Leu Lys Pro
        275                 280                 285

Cys Glu Phe Pro Gln Phe Lys Tyr Gly Arg Leu Tyr Tyr Glu Glu Ser
    290                 295                 300

Leu Arg Pro Asn Phe Pro Val Ser Ile Gly Asn Lys Tyr Ser Tyr Lys
305                 310                 315                 320

Cys Asp Asn Gly Phe Ser Pro Pro Ser Gly Tyr Ser Trp Asp Tyr Leu
                325                 330                 335

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

Cys Val Phe His Tyr Val Glu Asn Gly Asp Ser Ala Tyr Trp Glu Lys
        355                 360                 365

Val Tyr Val Gln Gly Gln Ser Leu Lys Val Gln Cys Tyr Asn Gly Tyr
    370                 375                 380

Ser Leu Gln Asn Gly Gln Asp Thr Met Thr Cys Thr Glu Asn Gly Trp
385                 390                 395                 400

Ser Pro Pro Pro Lys Cys Ile Arg Ile Lys Thr Cys Ser Ala Ser Asp
                405                 410                 415

Ile His Ile Asp Asn Gly Phe Leu Ser Glu Ser Ser Ser Ile Tyr Ala
            420                 425                 430

Leu Asn Arg Glu Thr Ser Tyr Arg Cys Lys Gln Gly Tyr Val Thr Asn
        435                 440                 445

Thr Gly Glu Ile Ser Gly Ser Ile Thr Cys Leu Gln Asn Gly Trp Ser
    450                 455                 460

Pro Gln Pro Ser Cys Ile Lys Ser Arg Asp Ser Thr Gly Lys Cys Gly
465                 470                 475                 480

Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile Thr Ser Leu Ser Leu Pro
                485                 490                 495

Val Tyr Glu Pro Leu Ser Ser Val Glu Tyr Gln Cys Gln Lys Tyr Tyr
            500                 505                 510
```

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Leu Leu Lys Gly Lys Lys Thr Ile Thr Cys Arg Asn Gly Lys Trp Ser
        515                 520                 525

Glu Pro Pro Thr Cys Leu His Ala Cys Val Ile Pro Glu Asn Ile Met
    530                 535                 540

Glu Ser His Asn Ile Ile Leu Lys Trp Arg His Thr Glu Lys Ile Tyr
545                 550                 555                 560

Ser His Ser Gly Glu Asp Ile Glu Phe Gly Cys Lys Tyr Gly Tyr Tyr
                565                 570                 575

Lys Ala Arg Asp Ser Pro Pro Phe Arg Thr Lys Cys Ile Asn Gly Thr
            580                 585                 590

Ile Asn Tyr Pro Thr Cys Val
        595
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<210> 45
<211> 2106
<212> DNA
<213> Artificial Sequence

<220>
<223> engineered fH SCR1-4, 6-8, 17-20

<220>
<221> CDS
<222> (1)..(2106)

<400> 45

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atg aga ctt cta gca aag att att tgc ctt atg tta tgg gct att tgt         48
Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1               5                   10                  15

gta gca gaa gat tgc aat gaa ctt cct cca aga aga aat aca gaa att         96
Val Ala Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile
            20                  25                  30

ctg aca ggt tcc tgg tct gac caa aca tat cca gaa ggc acc cag gct        144
Leu Thr Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala
        35                  40                  45

atc tat aaa tgc cgc cct gga tat aga tct ctt gga aat ata ata atg        192
Ile Tyr Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Ile Ile Met
    50                  55                  60

gta tgc agg aag gga gaa tgg gtt gct ctt aat cca tta agg aaa tgt        240
Val Cys Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys
65                  70                  75                  80

cag aaa agg ccc tgt gga cat cct gga gat act cct ttt ggt act ttt        288
Gln Lys Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe
                85                  90                  95
```

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acc ctt aca gga gga aat gtg ttt gaa tat ggt gta aaa gct gtg tat        336
Thr Leu Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr
            100                 105                 110

aca tgt aat gag ggg tat caa ttg cta ggt gag att aat tac cgt gaa        384
Thr Cys Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu
        115                 120                 125

tgt gac aca gat gga tgg acc aat gat att cct ata tgt gaa gtt gtg        432
Cys Asp Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val
    130                 135                 140

aag tgt tta cca gtg aca gca cca gag aat gga aaa att gtc agt agt        480
Lys Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser
145                 150                 155                 160

gca atg gaa cca gat cgg gaa tac cat ttt gga caa gca gta cgg ttt        528
Ala Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe
                165                 170                 175

gta tgt aac tca ggc tac aag att gaa gga gat gaa gaa atg cat tgt        576
Val Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys
            180                 185                 190

tca gac gat ggt ttt tgg agt aaa gag aaa cca aag tgt gtg gaa att        624
Ser Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile
        195                 200                 205

tca tgc aaa tcc cca gat gtt ata aat gga tct cct ata tct cag aag        672
Ser Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys
    210                 215                 220

att att tat aag gag aat gaa cga ttt caa tat aaa tgt aac atg ggt        720
Ile Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly
225                 230                 235                 240

tat gaa tac agt gaa aga gga gat gct gta tgc act gaa tct gga tgg        768
Tyr Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp
                245                 250                 255

cgt ccg ttg cct tca tgt gaa gaa aaa tca acc ttg aaa cct tgt gat        816
Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Thr Leu Lys Pro Cys Asp
            260                 265                 270

tat cca gac att aaa cat gga ggt cta tat cat gag aat atg cgt aga        864
Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr His Glu Asn Met Arg Arg
        275                 280                 285

cca tac ttt cca gta gct gta gga aaa tat tac tcc tat tac tgt gat        912
Pro Tyr Phe Pro Val Ala Val Gly Lys Tyr Tyr Ser Tyr Tyr Cys Asp
    290                 295                 300

gaa cat ttt gag act ccg tca gga agt tac tgg gat cac att cat tgc        960
Glu His Phe Glu Thr Pro Ser Gly Ser Tyr Trp Asp His Ile His Cys
305                 310                 315                 320

aca caa gat gga tgg tcg cca gca gta cca tgc ctc aga aaa tgt tat       1008
Thr Gln Asp Gly Trp Ser Pro Ala Val Pro Cys Leu Arg Lys Cys Tyr
                325                 330                 335

ttt cct tat ttg gaa aat gga tat aat caa aat tat gga aga aag ttt       1056
Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln Asn Tyr Gly Arg Lys Phe
            340                 345                 350
```

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gta cag ggt aaa tct ata gac gtt gcc tgc cat cct ggc tac gct ctt       1104
Val Gln Gly Lys Ser Ile Asp Val Ala Cys His Pro Gly Tyr Ala Leu
        355                 360                 365

cca aaa gcg cag acc aca gtt aca tgt atg gag aat ggc tgg tct cct       1152
Pro Lys Ala Gln Thr Thr Val Thr Cys Met Glu Asn Gly Trp Ser Pro
    370                 375                 380

act ccc aga tgc atc cgt gtc aaa aca tgt tcc aaa tca agt ata gat       1200
Thr Pro Arg Cys Ile Arg Val Lys Thr Cys Ser Lys Ser Ser Ile Asp
385                 390                 395                 400

att gag aat ggg ttt att tct gaa tct cag tat aca tat gcc tta aaa       1248
Ile Glu Asn Gly Phe Ile Ser Glu Ser Gln Tyr Thr Tyr Ala Leu Lys
                405                 410                 415

gaa aaa gca aaa tat caa tgc aaa cta gga tat gta aca gca gat ggt       1296
Glu Lys Ala Lys Tyr Gln Cys Lys Leu Gly Tyr Val Thr Ala Asp Gly
            420                 425                 430

gaa aca tca gga tca att aca tgt ggg aaa gat gga tgg tca gct caa       1344
Glu Thr Ser Gly Ser Ile Thr Cys Gly Lys Asp Gly Trp Ser Ala Gln
        435                 440                 445

ccc acg tgc att aaa tct ata aaa aca gat tgt ctc agt tta cct agc       1392
Pro Thr Cys Ile Lys Ser Ile Lys Thr Asp Cys Leu Ser Leu Pro Ser
    450                 455                 460

ttt gaa aat gcc ata ccc atg gga gag aag aag gat gtg tat aag gcg       1440
Phe Glu Asn Ala Ile Pro Met Gly Glu Lys Lys Asp Val Tyr Lys Ala
465                 470                 475                 480

ggt gag caa gtg act tac act tgt gca aca tat tac aaa atg gat gga       1488
Gly Glu Gln Val Thr Tyr Thr Cys Ala Thr Tyr Tyr Lys Met Asp Gly
                485                 490                 495

gcc agt aat gta aca tgc att aat agc aga tgg aca gga agg cca aca       1536
Ala Ser Asn Val Thr Cys Ile Asn Ser Arg Trp Thr Gly Arg Pro Thr
            500                 505                 510

tgc aga gac acc tcc tgt gtg aat ccg ccc aca gta caa aat gct tat       1584
Cys Arg Asp Thr Ser Cys Val Asn Pro Pro Thr Val Gln Asn Ala Tyr
        515                 520                 525

ata gtg tcg aga cag atg agt aaa tat cca tct ggt gag aga gta cgt       1632
Ile Val Ser Arg Gln Met Ser Lys Tyr Pro Ser Gly Glu Arg Val Arg
    530                 535                 540

tat caa tgt agg agc cct tat gaa atg ttt ggg gat gaa gaa gtg atg       1680
Tyr Gln Cys Arg Ser Pro Tyr Glu Met Phe Gly Asp Glu Glu Val Met
545                 550                 555                 560

tgt tta aat gga aac tgg acg gaa cca cct caa tgc aaa gat tct aca       1728
Cys Leu Asn Gly Asn Trp Thr Glu Pro Pro Gln Cys Lys Asp Ser Thr
                565                 570                 575

gga aaa tgt ggg ccc cct cca cct att gac aat ggg gac att act tca       1776
Gly Lys Cys Gly Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile Thr Ser
            580                 585                 590

ttc ccg ttg tca gta tat gct cca gct tca tca gtt gag tac caa tgc       1824
Phe Pro Leu Ser Val Tyr Ala Pro Ala Ser Ser Val Glu Tyr Gln Cys
```

595 600 605

cag aac ttg tat caa ctt gag ggt aac aag cga ata aca tgt aga aat 1872
Gln Asn Leu Tyr Gln Leu Glu Gly Asn Lys Arg Ile Thr Cys Arg Asn
610 615 620

gga caa tgg tca gaa cca cca aaa tgc tta cat ccg tgt gta ata tcc 1920
Gly Gln Trp Ser Glu Pro Pro Lys Cys Leu His Pro Cys Val Ile Ser
625 630 635 640

cga gaa att atg gaa aat tat aac ata gca tta agg tgg aca gcc aaa 1968
Arg Glu Ile Met Glu Asn Tyr Asn Ile Ala Leu Arg Trp Thr Ala Lys
645 650 655

cag aag ctt tat tcg aga aca ggt gaa tca gtt gaa ttt gtg tgt aaa 2016
Gln Lys Leu Tyr Ser Arg Thr Gly Glu Ser Val Glu Phe Val Cys Lys
660 665 670

cgg gga tat cgt ctt tca tca cgt tct cac aca ttg cga aca aca tgt 2064
Arg Gly Tyr Arg Leu Ser Ser Arg Ser His Thr Leu Arg Thr Thr Cys
675 680 685

tgg gat ggg aaa ctg gag tat cca act tgt gca aaa aga tag 2106
Trp Asp Gly Lys Leu Glu Tyr Pro Thr Cys Ala Lys Arg
690 695 700

<210> 46
<211> 701
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic Construct

<400> 46

Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1 5 10 15

Val Ala Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile
20 25 30

Leu Thr Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala
35 40 45

Ile Tyr Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Ile Ile Met
50 55 60

Val Cys Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys
65 70 75 80

Gln Lys Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe
85 90 95

Thr Leu Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr
100 105 110

```
Thr Cys Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu
        115                 120                 125

Cys Asp Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val
    130                 135                 140

Lys Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser
145                 150                 155                 160

Ala Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe
                165                 170                 175

Val Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys
            180                 185                 190

Ser Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile
        195                 200                 205

Ser Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys
    210                 215                 220

Ile Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly
225                 230                 235                 240

Tyr Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp
                245                 250                 255

Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Thr Leu Lys Pro Cys Asp
            260                 265                 270

Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr His Glu Asn Met Arg Arg
        275                 280                 285

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

Glu His Phe Glu Thr Pro Ser Gly Ser Tyr Trp Asp His Ile His Cys
305                 310                 315                 320

Thr Gln Asp Gly Trp Ser Pro Ala Val Pro Cys Leu Arg Lys Cys Tyr
                325                 330                 335

Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln Asn Tyr Gly Arg Lys Phe
            340                 345                 350

Val Gln Gly Lys Ser Ile Asp Val Ala Cys His Pro Gly Tyr Ala Leu
```

355 360 365

Pro Lys Ala Gln Thr Thr Val Thr Cys Met Glu Asn Gly Trp Ser Pro
370 375 380

Thr Pro Arg Cys Ile Arg Val Lys Thr Cys Ser Lys Ser Ser Ile Asp
385 390 395 400

Ile Glu Asn Gly Phe Ile Ser Glu Ser Gln Tyr Thr Tyr Ala Leu Lys
405 410 415

Glu Lys Ala Lys Tyr Gln Cys Lys Leu Gly Tyr Val Thr Ala Asp Gly
420 425 430

Glu Thr Ser Gly Ser Ile Thr Cys Gly Lys Asp Gly Trp Ser Ala Gln
435 440 445

Pro Thr Cys Ile Lys Ser Ile Lys Thr Asp Cys Leu Ser Leu Pro Ser
450 455 460

Phe Glu Asn Ala Ile Pro Met Gly Glu Lys Lys Asp Val Tyr Lys Ala
465 470 475 480

Gly Glu Gln Val Thr Tyr Thr Cys Ala Thr Tyr Tyr Lys Met Asp Gly
485 490 495

Ala Ser Asn Val Thr Cys Ile Asn Ser Arg Trp Thr Gly Arg Pro Thr
500 505 510

Cys Arg Asp Thr Ser Cys Val Asn Pro Pro Thr Val Gln Asn Ala Tyr
515 520 525

Ile Val Ser Arg Gln Met Ser Lys Tyr Pro Ser Gly Glu Arg Val Arg
530 535 540

Tyr Gln Cys Arg Ser Pro Tyr Glu Met Phe Gly Asp Glu Glu Val Met
545 550 555 560

Cys Leu Asn Gly Asn Trp Thr Glu Pro Pro Gln Cys Lys Asp Ser Thr
565 570 575

Gly Lys Cys Gly Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile Thr Ser
580 585 590

Phe Pro Leu Ser Val Tyr Ala Pro Ala Ser Ser Val Glu Tyr Gln Cys
595 600 605

Gln Asn Leu Tyr Gln Leu Glu Gly Asn Lys Arg Ile Thr Cys Arg Asn
610 615 620

Gly Gln Trp Ser Glu Pro Pro Lys Cys Leu His Pro Cys Val Ile Ser
625 630 635 640

Arg Glu Ile Met Glu Asn Tyr Asn Ile Ala Leu Arg Trp Thr Ala Lys
645 650 655

Gln Lys Leu Tyr Ser Arg Thr Gly Glu Ser Val Glu Phe Val Cys Lys
660 665 670

Arg Gly Tyr Arg Leu Ser Ser Arg Ser His Thr Leu Arg Thr Thr Cys
675 680 685

Trp Asp Gly Lys Leu Glu Tyr Pro Thr Cys Ala Lys Arg
690 695 700

<210> 47
<211> 2158
<212> DNA
<213> Artificial sequence

<220>
<223> hfH1-4.678.17-20 containing leader and 5' UTR

<400> 47
ggacgttgtg aacagagtta gctggtaaat gtcctcttaa aagatccaaa aaatgagact 60

tctagcaaag attatttgcc ttatgttatg ggctatttgt gtagcagaag attgcaatga 120

acttcctcca agaagaaata cagaaattct gacaggttcc tggtctgacc aaacatatcc 180

agaaggcacc caggctatct ataaatgccg ccctggatat agatctcttg gaaatataat 240

aatggtatgc aggaagggag aatgggttgc tcttaatcca ttaaggaaat gtcagaaaag 300

gccctgtgga catcctggag atactccttt tggtactttt acccttacag gaggaaatgt 360

gtttgaatat ggtgtaaaag ctgtgtatac atgtaatgag gggtatcaat tgctaggtga 420

gattaattac cgtgaatgtg acacagatgg atggaccaat gatattccta tatgtgaagt 480

tgtgaagtgt ttaccagtga cagcaccaga gaatggaaaa attgtcagta gtgcaatgga 540

accagatcgg gaataccatt ttggacaagc agtacggttt gtatgtaact caggctacaa 600

gattgaagga gatgaagaaa tgcattgttc agacgatggt ttttggagta aagagaaacc 660

aaagtgtgtg gaaatttcat gcaaatcccc agatgttata aatggatctc ctatatctca 720

gaagattatt tataaggaga atgaacgatt tcaatataaa tgtaacatgg gttatgaata 780

cagtgaaaga ggagatgctg tatgcactga atctggatgg cgtccgttgc cttcatgtga 840

agaaaaatca accttgaaac cttgtgatta tccagacatt aaacatggag gtctatatca 900

tgagaatatg cgtagaccat actttccagt agctgtagga aaatattact cctattactg 960

tgatgaacat tttgagactc cgtcaggaag ttactgggat cacattcatt gcacacaaga 1020

tggatggtcg ccagcagtac catgcctcag aaaatgttat tttccttatt tggaaaatgg 1080

atataatcaa aattatggaa gaaagtttgt acagggtaaa tctatagacg ttgcctgcca 1140

tcctggctac gctcttccaa aagcgcagac cacagttaca tgtatggaga atggctggtc 1200

tcctactccc agatgcatcc gtgtcaaaac atgttccaaa tcaagtatag atattgagaa 1260

tgggtttatt tctgaatctc agtatacata tgccttaaaa gaaaaagcaa aatatcaatg 1320

caaactagga tatgtaacag cagatggtga aacatcagga tcaattacat gtgggaaaga 1380

tggatggtca gctcaaccca cgtgcattaa atctataaaa acagattgtc tcagtttacc 1440

tagctttgaa aatgccatac ccatgggaga gaagaaggat gtgtataagg cgggtgagca 1500

agtgacttac acttgtgcaa catattacaa aatggatgga gccagtaatg taacatgcat 1560

taatagcaga tggacaggaa ggccaacatg cagagacacc tcctgtgtga atccgcccac 1620

agtacaaaat gcttatatag tgtcgagaca gatgagtaaa tatccatctg gtgagagagt 1680

acgttatcaa tgtaggagcc cttatgaaat gtttggggat gaagaagtga tgtgtttaaa 1740

tggaaactgg acggaaccac ctcaatgcaa agattctaca ggaaaatgtg ggccccctcc 1800

acctattgac aatggggaca ttacttcatt cccgttgtca gtatatgctc cagcttcatc 1860

agttgagtac caatgccaga acttgtatca acttgagggt aacaagcgaa taacatgtag 1920

aaatggacaa tggtcagaac caccaaaatg cttacatccg tgtgtaatat cccgagaaat 1980

tatggaaaat tataacatag cattaaggtg gacagccaaa cagaagcttt attcgagaac 2040

aggtgaatca gttgaatttg tgtgtaaacg gggatatcgt ctttcatcac gttctcacac 2100

attgcgaaca acatgttggg atgggaaact ggagtatcca acttgtgcaa aaagatag 2158

<210> 48
<211> 701
<212> PRT
<213> Artificial Sequence

<220>
<223> hFH 1-4.678.17-20

<400> 48

Met Arg Leu Leu Ala Lys Ile Ile Cys Leu Met Leu Trp Ala Ile Cys
1 5 10 15

Val Ala Glu Asp Cys Asn Glu Leu Pro Pro Arg Arg Asn Thr Glu Ile
20 25 30

Leu Thr Gly Ser Trp Ser Asp Gln Thr Tyr Pro Glu Gly Thr Gln Ala
35 40 45

```
Ile Tyr Lys Cys Arg Pro Gly Tyr Arg Ser Leu Gly Asn Ile Ile Met
    50                  55                  60

Val Cys Arg Lys Gly Glu Trp Val Ala Leu Asn Pro Leu Arg Lys Cys
65                  70                  75                  80

Gln Lys Arg Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly Thr Phe
                85                  90                  95

Thr Leu Thr Gly Gly Asn Val Phe Glu Tyr Gly Val Lys Ala Val Tyr
            100                 105                 110

Thr Cys Asn Glu Gly Tyr Gln Leu Leu Gly Glu Ile Asn Tyr Arg Glu
        115                 120                 125

Cys Asp Thr Asp Gly Trp Thr Asn Asp Ile Pro Ile Cys Glu Val Val
    130                 135                 140

Lys Cys Leu Pro Val Thr Ala Pro Glu Asn Gly Lys Ile Val Ser Ser
145                 150                 155                 160

Ala Met Glu Pro Asp Arg Glu Tyr His Phe Gly Gln Ala Val Arg Phe
                165                 170                 175

Val Cys Asn Ser Gly Tyr Lys Ile Glu Gly Asp Glu Glu Met His Cys
            180                 185                 190

Ser Asp Asp Gly Phe Trp Ser Lys Glu Lys Pro Lys Cys Val Glu Ile
        195                 200                 205

Ser Cys Lys Ser Pro Asp Val Ile Asn Gly Ser Pro Ile Ser Gln Lys
    210                 215                 220

Ile Ile Tyr Lys Glu Asn Glu Arg Phe Gln Tyr Lys Cys Asn Met Gly
225                 230                 235                 240

Tyr Glu Tyr Ser Glu Arg Gly Asp Ala Val Cys Thr Glu Ser Gly Trp
                245                 250                 255

Arg Pro Leu Pro Ser Cys Glu Glu Lys Ser Thr Leu Lys Pro Cys Asp
            260                 265                 270

Tyr Pro Asp Ile Lys His Gly Gly Leu Tyr His Glu Asn Met Arg Arg
        275                 280                 285

Pro Tyr Phe Pro Val Ala Val Gly Lys Tyr Tyr Ser Tyr Tyr Cys Asp
```

290 295 300

Glu His Phe Glu Thr Pro Ser Gly Ser Tyr Trp Asp His Ile His Cys
305 310 315 320

Thr Gln Asp Gly Trp Ser Pro Ala Val Pro Cys Leu Arg Lys Cys Tyr
325 330 335

Phe Pro Tyr Leu Glu Asn Gly Tyr Asn Gln Asn Tyr Gly Arg Lys Phe
340 345 350

Val Gln Gly Lys Ser Ile Asp Val Ala Cys His Pro Gly Tyr Ala Leu
355 360 365

Pro Lys Ala Gln Thr Thr Val Thr Cys Met Glu Asn Gly Trp Ser Pro
370 375 380

Thr Pro Arg Cys Ile Arg Val Lys Thr Cys Ser Lys Ser Ser Ile Asp
385 390 395 400

Ile Glu Asn Gly Phe Ile Ser Glu Ser Gln Tyr Thr Tyr Ala Leu Lys
405 410 415

Glu Lys Ala Lys Tyr Gln Cys Lys Leu Gly Tyr Val Thr Ala Asp Gly
420 425 430

Glu Thr Ser Gly Ser Ile Thr Cys Gly Lys Asp Gly Trp Ser Ala Gln
435 440 445

Pro Thr Cys Ile Lys Ser Ile Lys Thr Asp Cys Leu Ser Leu Pro Ser
450 455 460

Phe Glu Asn Ala Ile Pro Met Gly Glu Lys Lys Asp Val Tyr Lys Ala
465 470 475 480

Gly Glu Gln Val Thr Tyr Thr Cys Ala Thr Tyr Tyr Lys Met Asp Gly
485 490 495

Ala Ser Asn Val Thr Cys Ile Asn Ser Arg Trp Thr Gly Arg Pro Thr
500 505 510

Cys Arg Asp Thr Ser Cys Val Asn Pro Pro Thr Val Gln Asn Ala Tyr
515 520 525

Ile Val Ser Arg Gln Met Ser Lys Tyr Pro Ser Gly Glu Arg Val Arg
530 535 540

Tyr Gln Cys Arg Ser Pro Tyr Glu Met Phe Gly Asp Glu Glu Val Met
545 550 555 560

Cys Leu Asn Gly Asn Trp Thr Glu Pro Pro Gln Cys Lys Asp Ser Thr
565 570 575

Gly Lys Cys Gly Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile Thr Ser
580 585 590

Phe Pro Leu Ser Val Tyr Ala Pro Ala Ser Ser Val Glu Tyr Gln Cys
595 600 605

Gln Asn Leu Tyr Gln Leu Glu Gly Asn Lys Arg Ile Thr Cys Arg Asn
610 615 620

Gly Gln Trp Ser Glu Pro Pro Lys Cys Leu His Pro Cys Val Ile Ser
625 630 635 640

Arg Glu Ile Met Glu Asn Tyr Asn Ile Ala Leu Arg Trp Thr Ala Lys
645 650 655

Gln Lys Leu Tyr Ser Arg Thr Gly Glu Ser Val Glu Phe Val Cys Lys
660 665 670

Arg Gly Tyr Arg Leu Ser Ser Arg Ser His Thr Leu Arg Thr Thr Cys
675 680 685

Trp Asp Gly Lys Leu Glu Tyr Pro Thr Cys Ala Lys Arg
690 695 700

<210> 49
<211> 27
<212> DNA
<213> Artificial sequence

<220>
<223> hfHdSCR5R truncation variant primer

<400> 49
tgatttttct tcacatgaag gcaacgg 27

<210> 50
<211> 28
<212> DNA
<213> Artificial Sequence

<220>
<223> hfHdSCR5F truncation primer

<400> 50
accttgaaac cttgtgatta tccagaca 28

<210> 51
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> hfHdSCR9-18R truncation variant primer

<400> 51
agatttaatg cacgtgggtt gagc 24

<210> 52
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> hfHdSCR9-18F truncation variant primer

<400> 52
aaagattcta caggaaaatg tgggcc 26

<210> 53
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> hfHdSCR9-16R truncation variant primer

<400> 53
agatttaatg cacgtgggtt gagc 24

<210> 54
<211> 31
<212> DNA
<213> Artificial sequence

<220>
<223> hfHdSCR9-16F truncation variant primer

<400> 54
ataaaaacag attgtctcag tttacctagc t 31

<210> 55
<211> 34
<212> DNA
<213> Artificial sequence

<220>
<223> pCBAGhfH-ORF F truncation variant primer

<400> 55
ttttggcaaa gaattggacg ttgtgaacag agtt 34

<210> 56
<211> 36

<212> DNA
<213> Artificial sequence

<220>
<223> CCTGAGGAGTGAATTCTATCTTTTTGCACAAGTTGG

<400> 56
cctgaggagt gaattctatc tttttgcaca agttgg 36

<210> 57
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> dSCR5R

<400> 57
tctcttttct tcacagaaag gctgagaact cc 32

<210> 58
<211> 30
<212> DNA
<213> Artificial sequence

<220>
<223> dSCR5F truncation varient primer

<400> 58
accttgaaac catgtgaatt tccacaattc 30

<210> 59
<211> 23
<212> DNA
<213> Artificial sequence

<220>
<223> dSCR9-18F truncation varient primer

<400> 59
cgagactcaa cagggaaatg tgg 23

<210> 60
<211> 25
<212> DNA
<213> Artificial sequence

<220>
<223> dSCR9-18R truncation primer

<400> 60
agacttaatg catgagggtt gaggt 25

<210> 61
<211> 140
<212> DNA
<213> Artificial sequence

<220>
<223> AAV 5' ITR

<400> 61
ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc ccgggcgtcg ggcgacctttt 60

ggtcgcccgg cctcagtgag cgagcgagcg cgcagagagg gagtggccaa ctccatcact 120

aggggttcct tgtagttaat 140

<210> 62
<211> 140
<212> DNA
<213> Artificial sequence

<220>
<223> AAV 3' ITR

<400> 62
attaactaca aggaacccct agtgatggag ttggccactc cctctctgcg cgctcgctcg 60

ctcactgagg ccgggcgacc aaaggtcgcc cgacgcccgg gctttgcccg ggcggcctca 120

gtgagcgagc gagcgcgcag 140

<210> 63
<211> 36
<212> DNA
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<220>
<223> Hinc II 5'ITR F insertion primer

<400> 63
aagtgccacc tggtcgacgc tgcgcgctcg ctcgct 36

<210> 64
<211> 38
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<220>
<223> Hinc II 5'ITR R insertion primer

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tcaataatca atgtcgacat taactacaag gaacccct 38

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<223> Pst I 3'ITR F insertion primer

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gaagatccct cgacctgcag attaactaca aggaacccct 40

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<223> Pst I 3'ITR R insertion primer

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acgccaagct tgggctgcag ctgcgcgctc gctcgctc 38

<210> 67
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<220>
<223> mFH primer 21st exon + intron

<400> 67
gcggccgccc tatccattag tgagtgtgg 29

<210> 68
<211> 27
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<223> R primer mFH 21st exon + intron

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ctcgaggaca gcgatgtaag aacaatc 27

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<223> F primer mFH SCR20 (exon 22)

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ggtaccaagc ttattgacca gctacagaca gta 33

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<223> R primer mFH SCR20 (exon 22)

<400> 70
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<210> 71
<211> 38
<212> DNA

<213> Artificial sequence

<220>
<223> F primer W1183R mutation hFH

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<211> 38
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<223> R primer W1183R mutation

<400> 72
cagtgtgtct ccttttgaga attatattgt gtgattcc 38

<210> 73
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<223> F Primer for 480 bp 3' probe

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<210> 74
<211> 20
<212> DNA
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<223> Neo-4 primer

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<210> 75
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aggtgagatg acaggagatc 20

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<400> 76
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<400> 77
gggtgggatt agataaatgc c 21

<210> 78
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1 5 10 15

caa att atg aga ctg tca gca aga att att tgg ctt ata tta tgg act 96
Gln Ile Met Arg Leu Ser Ala Arg Ile Ile Trp Leu Ile Leu Trp Thr
20 25 30

gtt tgt gca gca gaa gat tgt aaa ggt cct cct cca aga gaa aat tca 144
Val Cys Ala Ala Glu Asp Cys Lys Gly Pro Pro Pro Arg Glu Asn Ser
35 40 45

gaa att ctc tca ggc tcg tgg tca gaa caa cta tat cca gaa ggc acc 192
Glu Ile Leu Ser Gly Ser Trp Ser Glu Gln Leu Tyr Pro Glu Gly Thr
50 55 60

cag gct acc tac aaa tgc cgc cct gga tac cga aca ctt ggc act att 240
Gln Ala Thr Tyr Lys Cys Arg Pro Gly Tyr Arg Thr Leu Gly Thr Ile
65 70 75 80

gta aaa gta tgc aag aat gga aaa tgg gtg gcg tct aac cca tcc agg 288
Val Lys Val Cys Lys Asn Gly Lys Trp Val Ala Ser Asn Pro Ser Arg
85 90 95

ata tgt cgg aaa aag cct tgt ggg cat ccc gga gac aca ccc ttt ggg 336
Ile Cys Arg Lys Lys Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly
100 105 110

tcc ttt agg ctg gca gtt gga tct caa ttt gag ttt ggt gca aag gtt 384

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Ser Phe Arg Leu Ala Val Gly Ser Gln Phe Glu Phe Gly Ala Lys Val
        115                 120                 125

gtt tat acc tgt gat gat ggg tat caa cta tta ggt gaa att gat tac        432
Val Tyr Thr Cys Asp Asp Gly Tyr Gln Leu Leu Gly Glu Ile Asp Tyr
    130                 135                 140

cgt gaa tgt ggt gca gat ggg tgg atc aat gat att cca cta tgt gaa        480
Arg Glu Cys Gly Ala Asp Gly Trp Ile Asn Asp Ile Pro Leu Cys Glu
145                 150                 155                 160

gtt gtg aag tgt cta cct gtg aca gaa ctc gag aat gga aga att gtg        528
Val Val Lys Cys Leu Pro Val Thr Glu Leu Glu Asn Gly Arg Ile Val
                165                 170                 175

agt ggt gca gca gaa aca gac cag gaa tac tat ttt gga cag gtg gtg        576
Ser Gly Ala Ala Glu Thr Asp Gln Glu Tyr Tyr Phe Gly Gln Val Val
            180                 185                 190

cgg ttt gaa tgc aat tca ggc ttc aag att gaa gga cat aag gaa att        624
Arg Phe Glu Cys Asn Ser Gly Phe Lys Ile Glu Gly His Lys Glu Ile
        195                 200                 205

cat tgc tca gaa aat ggc ctt tgg agc aat gaa aag cca cga tgt gtg        672
His Cys Ser Glu Asn Gly Leu Trp Ser Asn Glu Lys Pro Arg Cys Val
    210                 215                 220

gaa att ctc tgc aca cca ccg cga gtg gaa aat gga gat ggt ata aat        720
Glu Ile Leu Cys Thr Pro Pro Arg Val Glu Asn Gly Asp Gly Ile Asn
225                 230                 235                 240

gtg aaa cca gtt tac aag gag aat gaa aga tac cac tat aag tgt aag        768
Val Lys Pro Val Tyr Lys Glu Asn Glu Arg Tyr His Tyr Lys Cys Lys
                245                 250                 255

cat ggt tat gtg ccc aaa gaa aga ggg gat gcc gtc tgc aca ggc tct        816
His Gly Tyr Val Pro Lys Glu Arg Gly Asp Ala Val Cys Thr Gly Ser
            260                 265                 270

gga tgg agt tct cag cct ttc tgt gaa gaa aag aga tgc tca cct cct        864
Gly Trp Ser Ser Gln Pro Phe Cys Glu Glu Lys Arg Cys Ser Pro Pro
        275                 280                 285

tat att cta aat ggt atc tac aca cct cac agg att ata cac aga agt        912
Tyr Ile Leu Asn Gly Ile Tyr Thr Pro His Arg Ile Ile His Arg Ser
    290                 295                 300

gat gat gaa atc aga tat gaa tgt aat tat ggc ttc tat cct gta act        960
Asp Asp Glu Ile Arg Tyr Glu Cys Asn Tyr Gly Phe Tyr Pro Val Thr
305                 310                 315                 320

gga tca act gtt tca aag tgt aca ccc act ggc tgg atc cct gtt cca       1008
Gly Ser Thr Val Ser Lys Cys Thr Pro Thr Gly Trp Ile Pro Val Pro
                325                 330                 335

aga tgt acc ttg aaa cca tgt gaa ttt cca caa ttc aaa tat gga cgt       1056
Arg Cys Thr Leu Lys Pro Cys Glu Phe Pro Gln Phe Lys Tyr Gly Arg
            340                 345                 350

ctg tat tat gaa gag agc ctg aga ccc aac ttc cca gta tct ata gga       1104
Leu Tyr Tyr Glu Glu Ser Leu Arg Pro Asn Phe Pro Val Ser Ile Gly
        355                 360                 365
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aat aag tac agc tat aag tgt gac aac ggg ttt tca cca cct tct ggg       1152
Asn Lys Tyr Ser Tyr Lys Cys Asp Asn Gly Phe Ser Pro Pro Ser Gly
    370                 375                 380

tat tcc tgg gac tac ctt cgt tgc aca gca caa ggg tgg gag cct gaa       1200
Tyr Ser Trp Asp Tyr Leu Arg Cys Thr Ala Gln Gly Trp Glu Pro Glu
385                 390                 395                 400

gtc cca tgc gtc agg aaa tgt gtt ttc cat tat gtg gag aat gga gac       1248
Val Pro Cys Val Arg Lys Cys Val Phe His Tyr Val Glu Asn Gly Asp
                405                 410                 415

tct gca tac tgg gaa aaa gta tat gtg cag ggt cag tct tta aaa gtc       1296
Ser Ala Tyr Trp Glu Lys Val Tyr Val Gln Gly Gln Ser Leu Lys Val
            420                 425                 430

cag tgt tac aat ggc tat agt ctt caa aat ggt caa gac aca atg aca       1344
Gln Cys Tyr Asn Gly Tyr Ser Leu Gln Asn Gly Gln Asp Thr Met Thr
        435                 440                 445

tgt aca gag aat ggc tgg tcc cct cct ccc aaa tgc atc cgt atc aag       1392
Cys Thr Glu Asn Gly Trp Ser Pro Pro Pro Lys Cys Ile Arg Ile Lys
    450                 455                 460

aca tgt tca gca tca gat ata cac att gac aat gga ttt ctt tct gaa       1440
Thr Cys Ser Ala Ser Asp Ile His Ile Asp Asn Gly Phe Leu Ser Glu
465                 470                 475                 480

tct tct tct ata tat gct cta aat aga gaa aca tcc tat aga tgt aag       1488
Ser Ser Ser Ile Tyr Ala Leu Asn Arg Glu Thr Ser Tyr Arg Cys Lys
                485                 490                 495

cag gga tat gtg aca aat act gga gaa ata tca gga tca ata act tgc       1536
Gln Gly Tyr Val Thr Asn Thr Gly Glu Ile Ser Gly Ser Ile Thr Cys
            500                 505                 510

ctt caa aat gga tgg tca cct caa ccc tca tgc att aag tct tgt gat       1584
Leu Gln Asn Gly Trp Ser Pro Gln Pro Ser Cys Ile Lys Ser Cys Asp
        515                 520                 525

atg cct gta ttt gag aat tct ata act aag aat act agg aca tgg ttt       1632
Met Pro Val Phe Glu Asn Ser Ile Thr Lys Asn Thr Arg Thr Trp Phe
    530                 535                 540

aag ctc aat gac aaa tta gac tat gaa tgt ctc gtt gga ttt gaa aat       1680
Lys Leu Asn Asp Lys Leu Asp Tyr Glu Cys Leu Val Gly Phe Glu Asn
545                 550                 555                 560

gaa tat aaa cat acc aaa ggc tct ata aca tgt act tat tat gga tgg       1728
Glu Tyr Lys His Thr Lys Gly Ser Ile Thr Cys Thr Tyr Tyr Gly Trp
                565                 570                 575

tct gat aca ccc tca tgt tat gaa aga gaa tgc agt gtt ccc act cta       1776
Ser Asp Thr Pro Ser Cys Tyr Glu Arg Glu Cys Ser Val Pro Thr Leu
            580                 585                 590

gac cga aaa cta gtc gtt tcc ccc aga aaa gaa aaa tac aga gtt gga       1824
Asp Arg Lys Leu Val Val Ser Pro Arg Lys Glu Lys Tyr Arg Val Gly
        595                 600                 605

gat ttg ttg gaa ttc tcc tgc cat tca gga cac aga gtt ggg cca gat       1872
Asp Leu Leu Glu Phe Ser Cys His Ser Gly His Arg Val Gly Pro Asp
    610                 615                 620
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tca gtg caa tgc tac cac ttt gga tgg tct cct ggt ttc cct aca tgt       1920
Ser Val Gln Cys Tyr His Phe Gly Trp Ser Pro Gly Phe Pro Thr Cys
625                 630                 635                 640

aaa ggt caa gta gca tca tgt gca cca cct ctt gaa att ctt aat ggg       1968
Lys Gly Gln Val Ala Ser Cys Ala Pro Pro Leu Glu Ile Leu Asn Gly
                645                 650                 655

gaa att aat gga gca aaa aaa gtt gaa tac agc cat ggt gaa gtg gtg       2016
Glu Ile Asn Gly Ala Lys Lys Val Glu Tyr Ser His Gly Glu Val Val
            660                 665                 670

aaa tat gat tgc aaa cct aga ttc cta ctg aag gga ccc aat aaa atc       2064
Lys Tyr Asp Cys Lys Pro Arg Phe Leu Leu Lys Gly Pro Asn Lys Ile
        675                 680                 685

cag tgt gtt gat ggg aat tgg aca acc ttg cct gta tgt att gag gag       2112
Gln Cys Val Asp Gly Asn Trp Thr Thr Leu Pro Val Cys Ile Glu Glu
    690                 695                 700

gag aga aca tgt gga gac att cct gaa ctt gaa cat ggc tct gcc aag       2160
Glu Arg Thr Cys Gly Asp Ile Pro Glu Leu Glu His Gly Ser Ala Lys
705                 710                 715                 720

tgt tct gtt cct ccc tac cac cat gga gat tca gtg gag ttc att tgt       2208
Cys Ser Val Pro Pro Tyr His His Gly Asp Ser Val Glu Phe Ile Cys
                725                 730                 735

gaa gaa aac ttc aca atg att gga cat ggg tca gtt tct tgc att agt       2256
Glu Glu Asn Phe Thr Met Ile Gly His Gly Ser Val Ser Cys Ile Ser
            740                 745                 750

gga aaa tgg acc cag ctt cct aaa tgt gtt gca aca gac caa ctg gag       2304
Gly Lys Trp Thr Gln Leu Pro Lys Cys Val Ala Thr Asp Gln Leu Glu
        755                 760                 765

aag tgt aga gtg ctg aag tca act ggc ata gaa gca ata aaa cca aaa       2352
Lys Cys Arg Val Leu Lys Ser Thr Gly Ile Glu Ala Ile Lys Pro Lys
    770                 775                 780

ttg act gaa ttt acg cat aac tcc acc atg gat tac aaa tgt aga gac       2400
Leu Thr Glu Phe Thr His Asn Ser Thr Met Asp Tyr Lys Cys Arg Asp
785                 790                 795                 800

aag cag gag tac gaa cgc tca atc tgt atc aat gga aaa tgg gat cct       2448
Lys Gln Glu Tyr Glu Arg Ser Ile Cys Ile Asn Gly Lys Trp Asp Pro
                805                 810                 815

gaa cca aac tgt aca agc aaa aca tcc tgc cct cct cca ccg cag att       2496
Glu Pro Asn Cys Thr Ser Lys Thr Ser Cys Pro Pro Pro Pro Gln Ile
            820                 825                 830

cca aat acc caa gtg att gaa acc acc gtg aaa tac ttg gat gga gaa       2544
Pro Asn Thr Gln Val Ile Glu Thr Thr Val Lys Tyr Leu Asp Gly Glu
        835                 840                 845

aaa tta tct gtt ctt tgc caa gac aat tac cta act cag gac tca gaa       2592
Lys Leu Ser Val Leu Cys Gln Asp Asn Tyr Leu Thr Gln Asp Ser Glu
    850                 855                 860

gaa atg gtg tgc aaa gat gga agg tgg cag tca tta cct cgc tgc att       2640
Glu Met Val Cys Lys Asp Gly Arg Trp Gln Ser Leu Pro Arg Cys Ile
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865                 870                 875                 880

gaa aaa att cca tgt tcc cag ccc cct aca ata gaa cat gga tct att       2688
Glu Lys Ile Pro Cys Ser Gln Pro Pro Thr Ile Glu His Gly Ser Ile
                885                 890                 895

aat tta ccc aga tct tca gaa gaa agg aga gat tcc att gag tcc agc       2736
Asn Leu Pro Arg Ser Ser Glu Glu Arg Arg Asp Ser Ile Glu Ser Ser
            900                 905                 910

agt cat gaa cat gga act aca ttc agc tat gtc tgt gat gat ggt ttc       2784
Ser His Glu His Gly Thr Thr Phe Ser Tyr Val Cys Asp Asp Gly Phe
        915                 920                 925

agg ata cct gaa gaa aat agg ata acc tgc tac atg gga aaa tgg agc       2832
Arg Ile Pro Glu Glu Asn Arg Ile Thr Cys Tyr Met Gly Lys Trp Ser
    930                 935                 940

act cca cct cgc tgt gtt gga ctt cct tgt gga cct cca cct tca att       2880
Thr Pro Pro Arg Cys Val Gly Leu Pro Cys Gly Pro Pro Pro Ser Ile
945                 950                 955                 960

cct ctt ggt act gtt tct ctt gag cta gag agt tac caa cat ggg gaa       2928
Pro Leu Gly Thr Val Ser Leu Glu Leu Glu Ser Tyr Gln His Gly Glu
                965                 970                 975

gag gtt aca tac cat tgt tct aca ggc ttt gga att gat gga cca gca       2976
Glu Val Thr Tyr His Cys Ser Thr Gly Phe Gly Ile Asp Gly Pro Ala
            980                 985                 990

ttt att ata tgc gaa gga gga aag  tgg tct gac cca cca  aaa tgc ata     3024
Phe Ile Ile Cys Glu Gly Gly Lys  Trp Ser Asp Pro Pro  Lys Cys Ile
        995                 1000                1005

aaa acg  gat tgt gac gtt tta  ccc aca gtt aaa aat  gcc ata ata       3069
Lys Thr  Asp Cys Asp Val Leu  Pro Thr Val Lys Asn  Ala Ile Ile
    1010                1015                1020

aga gga  aag agc aaa aaa tca  tat agg aca gga gaa  caa gtg aca       3114
Arg Gly  Lys Ser Lys Lys Ser  Tyr Arg Thr Gly Glu  Gln Val Thr
    1025                1030                1035

ttc aga  tgt caa tct cct tat  caa atg aat ggc tca  gac act gtg       3159
Phe Arg  Cys Gln Ser Pro Tyr  Gln Met Asn Gly Ser  Asp Thr Val
    1040                1045                1050

aca tgt  gtt aat agt cgg tgg  att gga cag cca gta  tgc aaa gat       3204
Thr Cys  Val Asn Ser Arg Trp  Ile Gly Gln Pro Val  Cys Lys Asp
    1055                1060                1065

aat tcc  tgt gtg gat cca cca  cat gtg cca aat gct  act ata gta       3249
Asn Ser  Cys Val Asp Pro Pro  His Val Pro Asn Ala  Thr Ile Val
    1070                1075                1080

aca agg  acc aag aat aaa tat  cta cat ggt gac aga  gta cgt tat       3294
Thr Arg  Thr Lys Asn Lys Tyr  Leu His Gly Asp Arg  Val Arg Tyr
    1085                1090                1095

gaa tgt  aat aaa cct ttg gaa  cta ttt ggg caa gtg  gaa gtg atg       3339
Glu Cys  Asn Lys Pro Leu Glu  Leu Phe Gly Gln Val  Glu Val Met
    1100                1105                1110

tgt gaa  aat ggg ata tgg aca  gaa aaa cca aag tgc  cga gac tca       3384
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Cys Glu  Asn Gly Ile Trp Thr  Glu Lys Pro Lys Cys  Arg Asp Ser
    1115                1120                1125

aca ggg  aaa tgt ggg cct cct  cca cct att gac aat  gga gac atc        3429
Thr Gly  Lys Cys Gly Pro Pro  Pro Pro Ile Asp Asn  Gly Asp Ile
    1130                1135                1140

acc tcc  ttg tca tta cca gta  tat gaa cca tta tca  tca gtt gaa        3474
Thr Ser  Leu Ser Leu Pro Val  Tyr Glu Pro Leu Ser  Ser Val Glu
    1145                1150                1155

tat caa  tgc cag aag tat tat  ctc ctt aag gga aag  aag aca ata        3519
Tyr Gln  Cys Gln Lys Tyr Tyr  Leu Leu Lys Gly Lys  Lys Thr Ile
    1160                1165                1170

aca tgt  aga aat gga aag tgg  tct gag cca cca aca  tgc tta cat        3564
Thr Cys  Arg Asn Gly Lys Trp  Ser Glu Pro Pro Thr  Cys Leu His
    1175                1180                1185

gca tgt  gta ata cca gaa aac  att atg gaa tca cac  aat ata att        3609
Ala Cys  Val Ile Pro Glu Asn  Ile Met Glu Ser His  Asn Ile Ile
    1190                1195                1200

ctc aaa  tgg aga cac act gaa  aag att tat tcc cat  tca ggg gag        3654
Leu Lys  Trp Arg His Thr Glu  Lys Ile Tyr Ser His  Ser Gly Glu
    1205                1210                1215

gat att  gaa ttt gga tgt aaa  tat gga tat tat aaa  gca aga gat        3699
Asp Ile  Glu Phe Gly Cys Lys  Tyr Gly Tyr Tyr Lys  Ala Arg Asp
    1220                1225                1230

tca ccg  cca ttt cgt aca aag  tgc att aat ggc acc  atc aat tat        3744
Ser Pro  Pro Phe Arg Thr Lys  Cys Ile Asn Gly Thr  Ile Asn Tyr
    1235                1240                1245

ccc act  tgt gta taa                                               3759
Pro Thr  Cys Val
    1250
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<210> 80
<211> 1252
<212> PRT
<213> Mus musculus

<400> 80

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Met Val Gln His Arg Phe Leu Leu Glu Ser Val Gly Pro Arg Lys Ile
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Gln Ile Met Arg Leu Ser Ala Arg Ile Ile Trp Leu Ile Leu Trp Thr
            20                  25                  30

Val Cys Ala Ala Glu Asp Cys Lys Gly Pro Pro Pro Arg Glu Asn Ser
        35                  40                  45

Glu Ile Leu Ser Gly Ser Trp Ser Glu Gln Leu Tyr Pro Glu Gly Thr
    50                  55                  60
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Gln Ala Thr Tyr Lys Cys Arg Pro Gly Tyr Arg Thr Leu Gly Thr Ile
65                  70                  75                  80

Val Lys Val Cys Lys Asn Gly Lys Trp Val Ala Ser Asn Pro Ser Arg
                85                  90                  95

Ile Cys Arg Lys Lys Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly
            100                 105                 110

Ser Phe Arg Leu Ala Val Gly Ser Gln Phe Glu Phe Gly Ala Lys Val
        115                 120                 125

Val Tyr Thr Cys Asp Asp Gly Tyr Gln Leu Leu Gly Glu Ile Asp Tyr
    130                 135                 140

Arg Glu Cys Gly Ala Asp Gly Trp Ile Asn Asp Ile Pro Leu Cys Glu
145                 150                 155                 160

Val Val Lys Cys Leu Pro Val Thr Glu Leu Glu Asn Gly Arg Ile Val
                165                 170                 175

Ser Gly Ala Ala Glu Thr Asp Gln Glu Tyr Tyr Phe Gly Gln Val Val
            180                 185                 190

Arg Phe Glu Cys Asn Ser Gly Phe Lys Ile Glu Gly His Lys Glu Ile
        195                 200                 205

His Cys Ser Glu Asn Gly Leu Trp Ser Asn Glu Lys Pro Arg Cys Val
    210                 215                 220

Glu Ile Leu Cys Thr Pro Pro Arg Val Glu Asn Gly Asp Gly Ile Asn
225                 230                 235                 240

Val Lys Pro Val Tyr Lys Glu Asn Glu Arg Tyr His Tyr Lys Cys Lys
                245                 250                 255

His Gly Tyr Val Pro Lys Glu Arg Gly Asp Ala Val Cys Thr Gly Ser
            260                 265                 270

Gly Trp Ser Ser Gln Pro Phe Cys Glu Glu Lys Arg Cys Ser Pro Pro
        275                 280                 285

Tyr Ile Leu Asn Gly Ile Tyr Thr Pro His Arg Ile Ile His Arg Ser
    290                 295                 300

Asp Asp Glu Ile Arg Tyr Glu Cys Asn Tyr Gly Phe Tyr Pro Val Thr
305                 310                 315                 320
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Gly Ser Thr Val Ser Lys Cys Thr Pro Thr Gly Trp Ile Pro Val Pro
                325                 330                 335

Arg Cys Thr Leu Lys Pro Cys Glu Phe Pro Gln Phe Lys Tyr Gly Arg
            340                 345                 350

Leu Tyr Tyr Glu Glu Ser Leu Arg Pro Asn Phe Pro Val Ser Ile Gly
        355                 360                 365

Asn Lys Tyr Ser Tyr Lys Cys Asp Asn Gly Phe Ser Pro Pro Ser Gly
    370                 375                 380

Tyr Ser Trp Asp Tyr Leu Arg Cys Thr Ala Gln Gly Trp Glu Pro Glu
385                 390                 395                 400

Val Pro Cys Val Arg Lys Cys Val Phe His Tyr Val Glu Asn Gly Asp
                405                 410                 415

Ser Ala Tyr Trp Glu Lys Val Tyr Val Gln Gly Gln Ser Leu Lys Val
            420                 425                 430

Gln Cys Tyr Asn Gly Tyr Ser Leu Gln Asn Gly Gln Asp Thr Met Thr
        435                 440                 445

Cys Thr Glu Asn Gly Trp Ser Pro Pro Pro Lys Cys Ile Arg Ile Lys
    450                 455                 460

Thr Cys Ser Ala Ser Asp Ile His Ile Asp Asn Gly Phe Leu Ser Glu
465                 470                 475                 480

Ser Ser Ser Ile Tyr Ala Leu Asn Arg Glu Thr Ser Tyr Arg Cys Lys
                485                 490                 495

Gln Gly Tyr Val Thr Asn Thr Gly Glu Ile Ser Gly Ser Ile Thr Cys
            500                 505                 510

Leu Gln Asn Gly Trp Ser Pro Gln Pro Ser Cys Ile Lys Ser Cys Asp
        515                 520                 525

Met Pro Val Phe Glu Asn Ser Ile Thr Lys Asn Thr Arg Thr Trp Phe
    530                 535                 540

Lys Leu Asn Asp Lys Leu Asp Tyr Glu Cys Leu Val Gly Phe Glu Asn
545                 550                 555                 560

Glu Tyr Lys His Thr Lys Gly Ser Ile Thr Cys Thr Tyr Tyr Gly Trp
                565                 570                 575
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Ser Asp Thr Pro Ser Cys Tyr Glu Arg Glu Cys Ser Val Pro Thr Leu
            580                 585                 590

Asp Arg Lys Leu Val Val Ser Pro Arg Lys Glu Lys Tyr Arg Val Gly
        595                 600                 605

Asp Leu Leu Glu Phe Ser Cys His Ser Gly His Arg Val Gly Pro Asp
    610                 615                 620

Ser Val Gln Cys Tyr His Phe Gly Trp Ser Pro Gly Phe Pro Thr Cys
625                 630                 635                 640

Lys Gly Gln Val Ala Ser Cys Ala Pro Pro Leu Glu Ile Leu Asn Gly
                645                 650                 655

Glu Ile Asn Gly Ala Lys Lys Val Glu Tyr Ser His Gly Glu Val Val
            660                 665                 670

Lys Tyr Asp Cys Lys Pro Arg Phe Leu Leu Lys Gly Pro Asn Lys Ile
        675                 680                 685

Gln Cys Val Asp Gly Asn Trp Thr Thr Leu Pro Val Cys Ile Glu Glu
    690                 695                 700

Glu Arg Thr Cys Gly Asp Ile Pro Glu Leu Glu His Gly Ser Ala Lys
705                 710                 715                 720

Cys Ser Val Pro Pro Tyr His His Gly Asp Ser Val Glu Phe Ile Cys
                725                 730                 735

Glu Glu Asn Phe Thr Met Ile Gly His Gly Ser Val Ser Cys Ile Ser
            740                 745                 750

Gly Lys Trp Thr Gln Leu Pro Lys Cys Val Ala Thr Asp Gln Leu Glu
        755                 760                 765

Lys Cys Arg Val Leu Lys Ser Thr Gly Ile Glu Ala Ile Lys Pro Lys
    770                 775                 780

Leu Thr Glu Phe Thr His Asn Ser Thr Met Asp Tyr Lys Cys Arg Asp
785                 790                 795                 800

Lys Gln Glu Tyr Glu Arg Ser Ile Cys Ile Asn Gly Lys Trp Asp Pro
                805                 810                 815

Glu Pro Asn Cys Thr Ser Lys Thr Ser Cys Pro Pro Pro Pro Gln Ile
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820 825 830

Pro Asn Thr Gln Val Ile Glu Thr Thr Val Lys Tyr Leu Asp Gly Glu
835 840 845

Lys Leu Ser Val Leu Cys Gln Asp Asn Tyr Leu Thr Gln Asp Ser Glu
850 855 860

Glu Met Val Cys Lys Asp Gly Arg Trp Gln Ser Leu Pro Arg Cys Ile
865 870 875 880

Glu Lys Ile Pro Cys Ser Gln Pro Pro Thr Ile Glu His Gly Ser Ile
885 890 895

Asn Leu Pro Arg Ser Ser Glu Glu Arg Arg Asp Ser Ile Glu Ser Ser
900 905 910

Ser His Glu His Gly Thr Thr Phe Ser Tyr Val Cys Asp Asp Gly Phe
915 920 925

Arg Ile Pro Glu Glu Asn Arg Ile Thr Cys Tyr Met Gly Lys Trp Ser
930 935 940

Thr Pro Pro Arg Cys Val Gly Leu Pro Cys Gly Pro Pro Pro Ser Ile
945 950 955 960

Pro Leu Gly Thr Val Ser Leu Glu Leu Glu Ser Tyr Gln His Gly Glu
965 970 975

Glu Val Thr Tyr His Cys Ser Thr Gly Phe Gly Ile Asp Gly Pro Ala
980 985 990

Phe Ile Ile Cys Glu Gly Gly Lys Trp Ser Asp Pro Pro Lys Cys Ile
995 1000 1005

Lys Thr Asp Cys Asp Val Leu Pro Thr Val Lys Asn Ala Ile Ile
1010 1015 1020

Arg Gly Lys Ser Lys Lys Ser Tyr Arg Thr Gly Glu Gln Val Thr
1025 1030 1035

Phe Arg Cys Gln Ser Pro Tyr Gln Met Asn Gly Ser Asp Thr Val
1040 1045 1050

Thr Cys Val Asn Ser Arg Trp Ile Gly Gln Pro Val Cys Lys Asp
1055 1060 1065

Asn Ser Cys Val Asp Pro Pro His Val Pro Asn Ala Thr Ile Val
1070 1075 1080

Thr Arg Thr Lys Asn Lys Tyr Leu His Gly Asp Arg Val Arg Tyr
1085 1090 1095

Glu Cys Asn Lys Pro Leu Glu Leu Phe Gly Gln Val Glu Val Met
1100 1105 1110

Cys Glu Asn Gly Ile Trp Thr Glu Lys Pro Lys Cys Arg Asp Ser
1115 1120 1125

Thr Gly Lys Cys Gly Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile
1130 1135 1140

Thr Ser Leu Ser Leu Pro Val Tyr Glu Pro Leu Ser Ser Val Glu
1145 1150 1155

Tyr Gln Cys Gln Lys Tyr Tyr Leu Leu Lys Gly Lys Lys Thr Ile
1160 1165 1170

Thr Cys Arg Asn Gly Lys Trp Ser Glu Pro Pro Thr Cys Leu His
1175 1180 1185

Ala Cys Val Ile Pro Glu Asn Ile Met Glu Ser His Asn Ile Ile
1190 1195 1200

Leu Lys Trp Arg His Thr Glu Lys Ile Tyr Ser His Ser Gly Glu
1205 1210 1215

Asp Ile Glu Phe Gly Cys Lys Tyr Gly Tyr Tyr Lys Ala Arg Asp
1220 1225 1230

Ser Pro Pro Phe Arg Thr Lys Cys Ile Asn Gly Thr Ile Asn Tyr
1235 1240 1245

Pro Thr Cys Val
1250

<210> 81
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<220>
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<222> (1)..(1800)

<400> 81

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atg gta cag cac aga ttt ctc ttg gag tca gtt ggt ccc aga aag atc          48
Met Val Gln His Arg Phe Leu Leu Glu Ser Val Gly Pro Arg Lys Ile
1               5                  10                  15

caa att atg aga ctg tca gca aga att att tgg ctt ata tta tgg act          96
Gln Ile Met Arg Leu Ser Ala Arg Ile Ile Trp Leu Ile Leu Trp Thr
            20                  25                  30

gtt tgt gca gca gaa gat tgt aaa ggt cct cct cca aga gaa aat tca         144
Val Cys Ala Ala Glu Asp Cys Lys Gly Pro Pro Pro Arg Glu Asn Ser
        35                  40                  45

gaa att ctc tca ggc tcg tgg tca gaa caa cta tat cca gaa ggc acc         192
Glu Ile Leu Ser Gly Ser Trp Ser Glu Gln Leu Tyr Pro Glu Gly Thr
    50                  55                  60

cag gct acc tac aaa tgc cgc cct gga tac cga aca ctt ggc act att         240
Gln Ala Thr Tyr Lys Cys Arg Pro Gly Tyr Arg Thr Leu Gly Thr Ile
65                  70                  75                  80

gta aaa gta tgc aag aat gga aaa tgg gtg gcg tct aac cca tcc agg         288
Val Lys Val Cys Lys Asn Gly Lys Trp Val Ala Ser Asn Pro Ser Arg
                85                  90                  95

ata tgt cgg aaa aag cct tgt ggg cat ccc gga gac aca ccc ttt ggg         336
Ile Cys Arg Lys Lys Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly
            100                 105                 110

tcc ttt agg ctg gca gtt gga tct caa ttt gag ttt ggt gca aag gtt         384
Ser Phe Arg Leu Ala Val Gly Ser Gln Phe Glu Phe Gly Ala Lys Val
        115                 120                 125

gtt tat acc tgt gat gat ggg tat caa cta tta ggt gaa att gat tac         432
Val Tyr Thr Cys Asp Asp Gly Tyr Gln Leu Leu Gly Glu Ile Asp Tyr
    130                 135                 140

cgt gaa tgt ggt gca gat ggg tgg atc aat gat att cca cta tgt gaa         480
Arg Glu Cys Gly Ala Asp Gly Trp Ile Asn Asp Ile Pro Leu Cys Glu
145                 150                 155                 160

gtt gtg aag tgt cta cct gtg aca gaa ctc gag aat gga aga att gtg         528
Val Val Lys Cys Leu Pro Val Thr Glu Leu Glu Asn Gly Arg Ile Val
                165                 170                 175

agt ggt gca gca gaa aca gac cag gaa tac tat ttt gga cag gtg gtg         576
Ser Gly Ala Ala Glu Thr Asp Gln Glu Tyr Tyr Phe Gly Gln Val Val
            180                 185                 190

cgg ttt gaa tgc aat tca ggc ttc aag att gaa gga cat aag gaa att         624
Arg Phe Glu Cys Asn Ser Gly Phe Lys Ile Glu Gly His Lys Glu Ile
        195                 200                 205

cat tgc tca gaa aat ggc ctt tgg agc aat gaa aag cca cga tgt gtg         672
His Cys Ser Glu Asn Gly Leu Trp Ser Asn Glu Lys Pro Arg Cys Val
    210                 215                 220

gaa att ctc tgc aca cca ccg cga gtg gaa aat gga gat ggt ata aat         720
Glu Ile Leu Cys Thr Pro Pro Arg Val Glu Asn Gly Asp Gly Ile Asn
225                 230                 235                 240
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gtg aaa cca gtt tac aag gag aat gaa aga tac cac tat aag tgt aag        768
Val Lys Pro Val Tyr Lys Glu Asn Glu Arg Tyr His Tyr Lys Cys Lys
                245                 250                 255

cat ggt tat gtg ccc aaa gaa aga ggg gat gcc gtc tgc aca ggc tct        816
His Gly Tyr Val Pro Lys Glu Arg Gly Asp Ala Val Cys Thr Gly Ser
            260                 265                 270

gga tgg agt tct cag cct ttc tgt gaa gaa aag aga acc ttg aaa cca        864
Gly Trp Ser Ser Gln Pro Phe Cys Glu Glu Lys Arg Thr Leu Lys Pro
        275                 280                 285

tgt gaa ttt cca caa ttc aaa tat gga cgt ctg tat tat gaa gag agc        912
Cys Glu Phe Pro Gln Phe Lys Tyr Gly Arg Leu Tyr Tyr Glu Glu Ser
    290                 295                 300

ctg aga ccc aac ttc cca gta tct ata gga aat aag tac agc tat aag        960
Leu Arg Pro Asn Phe Pro Val Ser Ile Gly Asn Lys Tyr Ser Tyr Lys
305                 310                 315                 320

tgt gac aac ggg ttt tca cca cct tct ggg tat tcc tgg gac tac ctt       1008
Cys Asp Asn Gly Phe Ser Pro Pro Ser Gly Tyr Ser Trp Asp Tyr Leu
                325                 330                 335

cgt tgc aca gca caa ggg tgg gag cct gaa gtc cca tgc gtc agg aaa       1056
Arg Cys Thr Ala Gln Gly Trp Glu Pro Glu Val Pro Cys Val Arg Lys
            340                 345                 350

tgt gtt ttc cat tat gtg gag aat gga gac tct gca tac tgg gaa aaa       1104
Cys Val Phe His Tyr Val Glu Asn Gly Asp Ser Ala Tyr Trp Glu Lys
        355                 360                 365

gta tat gtg cag ggt cag tct tta aaa gtc cag tgt tac aat ggc tat       1152
Val Tyr Val Gln Gly Gln Ser Leu Lys Val Gln Cys Tyr Asn Gly Tyr
    370                 375                 380

agt ctt caa aat ggt caa gac aca atg aca tgt aca gag aat ggc tgg       1200
Ser Leu Gln Asn Gly Gln Asp Thr Met Thr Cys Thr Glu Asn Gly Trp
385                 390                 395                 400

tcc cct cct ccc aaa tgc atc cgt atc aag aca tgt tca gca tca gat       1248
Ser Pro Pro Pro Lys Cys Ile Arg Ile Lys Thr Cys Ser Ala Ser Asp
                405                 410                 415

ata cac att gac aat gga ttt ctt tct gaa tct tct tct ata tat gct       1296
Ile His Ile Asp Asn Gly Phe Leu Ser Glu Ser Ser Ser Ile Tyr Ala
            420                 425                 430

cta aat aga gaa aca tcc tat aga tgt aag cag gga tat gtg aca aat       1344
Leu Asn Arg Glu Thr Ser Tyr Arg Cys Lys Gln Gly Tyr Val Thr Asn
        435                 440                 445

act gga gaa ata tca gga tca ata act tgc ctt caa aat gga tgg tca       1392
Thr Gly Glu Ile Ser Gly Ser Ile Thr Cys Leu Gln Asn Gly Trp Ser
    450                 455                 460

cct caa ccc tca tgc att aag tct cga gac tca aca ggg aaa tgt ggg       1440
Pro Gln Pro Ser Cys Ile Lys Ser Arg Asp Ser Thr Gly Lys Cys Gly
465                 470                 475                 480

cct cct cca cct att gac aat gga gac atc acc tcc ttg tca tta cca       1488
Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile Thr Ser Leu Ser Leu Pro
                485                 490                 495
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gta tat gaa cca tta tca tca gtt gaa tat caa tgc cag aag tat tat       1536
Val Tyr Glu Pro Leu Ser Ser Val Glu Tyr Gln Cys Gln Lys Tyr Tyr
            500                 505                 510

ctc ctt aag gga aag aag aca ata aca tgt aga aat gga aag tgg tct       1584
Leu Leu Lys Gly Lys Lys Thr Ile Thr Cys Arg Asn Gly Lys Trp Ser
        515                 520                 525

gag cca cca aca tgc tta cat gca tgt gta ata cca gaa aac att atg       1632
Glu Pro Pro Thr Cys Leu His Ala Cys Val Ile Pro Glu Asn Ile Met
    530                 535                 540

gaa tca cac aat ata att ctc aaa tgg aga cac act gaa aag att tat       1680
Glu Ser His Asn Ile Ile Leu Lys Trp Arg His Thr Glu Lys Ile Tyr
545                 550                 555                 560

tcc cat tca ggg gag gat att gaa ttt gga tgt aaa tat gga tat tat       1728
Ser His Ser Gly Glu Asp Ile Glu Phe Gly Cys Lys Tyr Gly Tyr Tyr
                565                 570                 575

aaa gca aga gat tca ccg cca ttt cgt aca aag tgc att aat ggc acc       1776
Lys Ala Arg Asp Ser Pro Pro Phe Arg Thr Lys Cys Ile Asn Gly Thr
            580                 585                 590

atc aat tat ccc act tgt gta taa                                      1800
Ile Asn Tyr Pro Thr Cys Val
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<210> 82
<211> 599
<212> PRT
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<223> Synthetic Construct

<400> 82

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Met Val Gln His Arg Phe Leu Leu Glu Ser Val Gly Pro Arg Lys Ile
1               5                   10                  15

Gln Ile Met Arg Leu Ser Ala Arg Ile Ile Trp Leu Ile Leu Trp Thr
            20                  25                  30

Val Cys Ala Ala Glu Asp Cys Lys Gly Pro Pro Pro Arg Glu Asn Ser
        35                  40                  45

Glu Ile Leu Ser Gly Ser Trp Ser Glu Gln Leu Tyr Pro Glu Gly Thr
    50                  55                  60

Gln Ala Thr Tyr Lys Cys Arg Pro Gly Tyr Arg Thr Leu Gly Thr Ile
65                  70                  75                  80

Val Lys Val Cys Lys Asn Gly Lys Trp Val Ala Ser Asn Pro Ser Arg
                85                  90                  95
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Ile Cys Arg Lys Lys Pro Cys Gly His Pro Gly Asp Thr Pro Phe Gly
            100                 105                 110

Ser Phe Arg Leu Ala Val Gly Ser Gln Phe Glu Phe Gly Ala Lys Val
        115                 120                 125

Val Tyr Thr Cys Asp Asp Gly Tyr Gln Leu Leu Gly Glu Ile Asp Tyr
    130                 135                 140

Arg Glu Cys Gly Ala Asp Gly Trp Ile Asn Asp Ile Pro Leu Cys Glu
145                 150                 155                 160

Val Val Lys Cys Leu Pro Val Thr Glu Leu Glu Asn Gly Arg Ile Val
                165                 170                 175

Ser Gly Ala Ala Glu Thr Asp Gln Glu Tyr Tyr Phe Gly Gln Val Val
            180                 185                 190

Arg Phe Glu Cys Asn Ser Gly Phe Lys Ile Glu Gly His Lys Glu Ile
        195                 200                 205

His Cys Ser Glu Asn Gly Leu Trp Ser Asn Glu Lys Pro Arg Cys Val
    210                 215                 220

Glu Ile Leu Cys Thr Pro Pro Arg Val Glu Asn Gly Asp Gly Ile Asn
225                 230                 235                 240

Val Lys Pro Val Tyr Lys Glu Asn Glu Arg Tyr His Tyr Lys Cys Lys
                245                 250                 255

His Gly Tyr Val Pro Lys Glu Arg Gly Asp Ala Val Cys Thr Gly Ser
            260                 265                 270

Gly Trp Ser Ser Gln Pro Phe Cys Glu Glu Lys Arg Thr Leu Lys Pro
        275                 280                 285

Cys Glu Phe Pro Gln Phe Lys Tyr Gly Arg Leu Tyr Tyr Glu Glu Ser
    290                 295                 300

Leu Arg Pro Asn Phe Pro Val Ser Ile Gly Asn Lys Tyr Ser Tyr Lys
305                 310                 315                 320

Cys Asp Asn Gly Phe Ser Pro Pro Ser Gly Tyr Ser Trp Asp Tyr Leu
                325                 330                 335

Arg Cys Thr Ala Gln Gly Trp Glu Pro Glu Val Pro Cys Val Arg Lys
            340                 345                 350
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Cys Val Phe His Tyr Val Glu Asn Gly Asp Ser Ala Tyr Trp Glu Lys
        355                 360                 365

Val Tyr Val Gln Gly Gln Ser Leu Lys Val Gln Cys Tyr Asn Gly Tyr
    370                 375                 380

Ser Leu Gln Asn Gly Gln Asp Thr Met Thr Cys Thr Glu Asn Gly Trp
385                 390                 395                 400

Ser Pro Pro Pro Lys Cys Ile Arg Ile Lys Thr Cys Ser Ala Ser Asp
                405                 410                 415

Ile His Ile Asp Asn Gly Phe Leu Ser Glu Ser Ser Ser Ile Tyr Ala
            420                 425                 430

Leu Asn Arg Glu Thr Ser Tyr Arg Cys Lys Gln Gly Tyr Val Thr Asn
        435                 440                 445

Thr Gly Glu Ile Ser Gly Ser Ile Thr Cys Leu Gln Asn Gly Trp Ser
    450                 455                 460

Pro Gln Pro Ser Cys Ile Lys Ser Arg Asp Ser Thr Gly Lys Cys Gly
465                 470                 475                 480

Pro Pro Pro Pro Ile Asp Asn Gly Asp Ile Thr Ser Leu Ser Leu Pro
                485                 490                 495

Val Tyr Glu Pro Leu Ser Ser Val Glu Tyr Gln Cys Gln Lys Tyr Tyr
            500                 505                 510

Leu Leu Lys Gly Lys Lys Thr Ile Thr Cys Arg Asn Gly Lys Trp Ser
        515                 520                 525

Glu Pro Pro Thr Cys Leu His Ala Cys Val Ile Pro Glu Asn Ile Met
    530                 535                 540

Glu Ser His Asn Ile Ile Leu Lys Trp Arg His Thr Glu Lys Ile Tyr
545                 550                 555                 560

Ser His Ser Gly Glu Asp Ile Glu Phe Gly Cys Lys Tyr Gly Tyr Tyr
                565                 570                 575

Lys Ala Arg Asp Ser Pro Pro Phe Arg Thr Lys Cys Ile Asn Gly Thr
            580                 585                 590

Ile Asn Tyr Pro Thr Cys Val
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595

<210> 83
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