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(71) Applicant *(for all designated States except US)*: **SYMPHOGEN A/S** [DK/DK]; Elektrovej, Bygning 375, DK-2800 Lyngby (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RASMUSSEN, Søren, Kofoed** [DK/DK]; Ternevej 22, DK-4000 Roskilde (DK). **TOLSTRUP, Anne, Bondgaard** [DK/DK]; Grønnegade 21, DK-3400 Hillerød (DK). **FREDERIKSEN, Søren, Bregenholt** [DK/DK]; Dalen 23, DK-2860 Søborg (DK). **HAURUM, John** [DK/DK]; Gustav Adolfsgade 6, 3. th., DK-2100 Copenhagen Ø (DK).

(74) Agent: **INSPICOS A/S**; Bøge Allé 5, P.O. Box 45, DK-2970 Hørsholm (DK).

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(54) Title: ANTI-RHESUS D RECOMBINANT POLYCLONAL ANTIBODY AND METHODS OF MANUFACTURE

(57) Abstract: The invention relates to a method for manufacturing an anti-RhD recombinant polyclonal antibody composition (anti-RhD rpAb). The method comprises obtaining a collection of cells transfected with a library of anti-RhD antibody expression vectors, wherein each cell in the collection is capable of expressing from a VH and VL comprising nucleic acid segment, one member of the library, which encodes a distinct member of anti-RhD recombinant polyclonal antibody composition and which is located at the same site in the genome of individual cells in said collection. The cells are cultured under suitable conditions for expression of the recombinant polyclonal antibody, which is obtained from the cells or culture supernatant. The nucleic acid segments encoding the anti-RhD rpAb is introduced into the cells by transfection with a library of vectors for site-specific integration. The present method is suitable for manufacturing anti-RhD rpAb, thereby making available a superior replacement of plasma-derived prophylactic and therapeutic immonoglobulin products.

ANTI-RHESUS D RECOMBINANT POLYCLONAL ANTIBODY AND METHODS OF MANUFACTURE

FIELD OF THE INVENTION

The present invention describes the production of an anti-Rhesus D recombinant polyclonal antibody (anti-RhD rpAb), as well as the general approach of generating a polyclonal working cell bank for later production of a desired polyclonal antibody. The invention also relates to libraries encoding anti-RhD rpAb and to cell lines producing anti-RhD rpAb. Further, the application describes pharmacological and diagnostic compositions comprising anti-RhD rpAb and their use in prophylaxis of hemolytic disease of the newborn (HDN), treatment of idiopathic thrombocytopenic purpura (ITP) and prevention of sensitization to the Rhesus D antigen after mistransfusions of RhD(+) blood to RhD(-) individuals.

BACKGROUND OF THE INVENTION

The Rhesus blood group antigens are located on transmembrane erythrocyte proteins encompassing the so-called C, c, E, e and D antigens. Approximately 16% of the Caucasian population is Rhesus D negative (RhD(-)) due to an inherited polymorphism. In addition, multiple genetic and serological variants of RhD exist (divided into category II- VII) of which RhD^{VI} is the most clinically relevant. Since category VI positive red blood cells (RBC) carry fewer of the various epitopes of the D protein than RBC of other categories, RhD^{VI}(+) individuals may form alloantibodies against RBC from other RhD positive (RhD(+)) individuals (Issitt, P.D. and Anstee, D.J., 1998. The Rh Blood Group System, Montgomery Scientific Publications, Durham, North Carolina, pp. 315-423).{Issitt & Anstee 1998 11809 /id}

RhD negativity in itself is not associated with any medical conditions, but has important medical implications when a RhD(-) female carries a RhD(+) or RhD^{VI}(+) fetus or a RhD^{VI}(+) female carries a RhD(+) fetus. Fetomaternal RhD alloimmunization may then occur if fetal erythrocytes enter the maternal circulation, usually perinatally (during delivery), and thereby causes the induction of a maternal anti-RhD antibody response. In subsequent pregnancies RhD-specific IgG-molecules from the mother will cross the placenta into the fetal circulation and mediate lysis of fetal erythrocytes, thereby causing Hemolytic Disease of Newborns (HDN). It has been estimated that on average 20% of RhD(-) women delivering a RhD(+) infant for the second time, and who are not protected appropriately with anti-D prophylaxis, will generate an anti-RhD antibody response. When untreated, approximately 30% of the newborn will have moderate anemia, jaundice, and hepatomegaly, and 20% develop severe anemia and hydrops fetalis, and severely affected newborns are at risk of neonatal death or permanent handicaps.

Polyclonal immunoglobulin preparations against RhD are used worldwide to prevent alloimmunization of pregnant RhD(-) and RhD^{VI}(+) women, thereby preventing hemolytic disease of the newborn. Polyclonal immunoglobulin preparations against RhD (anti-D) are currently obtained by pooling of blood plasma obtained from donors who have become hyperimmune, either through natural RhD alloimmunization or through vaccination of RhD negative volunteer males with RhD positive erythrocytes. The efficacy of anti-RhD immunoglobulin preparations for prophylaxis of HDN is well established and has been in routine use for many years. As a result this severe disease has become a rarity.

Nevertheless the underlying cause of the disease, i.e. alloimmunization of pregnant RhD(-) and RhD^{VI}(+) women, still remains and thus requires a continual supply of anti-D immunoglobulin preparations.

In addition to the prophylaxis of HDN, anti-D immunoglobulin has also proven useful in the treatment of idiopathic thrombocytopenic purpura (ITP) (George, J.N., 2002. Blood Rev. 16, 37-38). ITP is a hematological disorder, where autoantibodies results in an accelerated platelet clearance in the spleen and liver. Symptoms are decreased platelet levels resulting in bruising and bleeding. In severe cases the spleen is removed. This is however, not possible in infants due to severe side effect, thus alternative treatments like anti-D immunoglobulin are needed. Further, anti-D immunoglobulin is used after mistransfusions of RhD(+) blood to RhD(-) recipients in order to prevent sensitization to the Rhesus D antigen.

The current methods for production of anti-D require, as already mentioned, repeated immunization of an increasingly reluctant pool of donors for the production of high titer antiserum. There are also associated risk factors and technical problems, such as the use of Rhesus positive RBC for repeated immunization carrying the risk of transmission of viral diseases like hepatitis B, AIDS and other as yet unknown viruses. Further, there are problems with batch-to-batch variations. Therefore, an alternative method for production of anti-RhD antibodies is required.

Cellular approaches for generating anti-RhD monoclonal antibodies were first developed as an alternative to hyperimmune serum. These techniques encompassed Epstein Barr Virus transformation of lymphocytes creating B lymphoblastoid cell lines (Crawford et al. 1983. Lancet 1, 386-8). However, these cell lines are unstable and require extensive cloning. Production of human antibodies by the hybridoma technique was also restricted by the lack of a suitable human myeloma cell fusion partner (Kozbor, D. and Roder, J.C., 1983. Immunol. Today. 4, 72).

As substitute for these techniques a molecular approach involving repertoire cloning of V_H and V_L and the construction of phage display libraries was developed (Barbas, C.F. et al. 1991. Proc Natl. Acad. Sci. U S A 88, 7978-7982). The phage display technique was also

applicable for the isolation of Rhesus D antigen binders. A large number of monoclonal antibodies (mAbs) with Rhesus D antigen binding specificity have been isolated with this technique (WO 97/49809 and Siegel, D.L et al. 2002. Transfus. Clin. Biol. 9, 83-97).

Recent clinical trials with a recombinant anti-RhD^{VI} mAb have shown that it is possible to prevent RhD immunization after a large challenge with RhD(+) RBC (Miescher, S., et al. 2004, Blood 103, 4028-4035). However, the trial also showed that the mAb was less efficient with respect to clearance of the RBC than an anti-D immunoglobulin. The cause of this decreased clearance rate is not known. It is possible that a single antibody is not as efficient as the diversity of antibodies present in the anti-D immunoglobulin product, or that the presence of more than one immunoglobulin isotype i.e. IgG1 and IgG3 {Siegel, Czerwinski, et al. 2002 10320 /id}increases RBC clearance.

In addition to the efficiency issue, another issue with respect to HDN prophylaxis is the situation where a RhD^{VI}(+) female carries a RhD(+) fetus. In this situation an anti-RhD^{VI} mAb will not be able to prevent alloimmunization of the female. Thus, in order to protect both RhD(-) and RhD^{VI}(+) females, a product with antibodies against Rhesus D category VI antigen as well as antibodies that do not bind category VI antigen but other common Rhesus D antigens is needed.

Another possible issue with mAbs is that they might be immunogenic. Although the mAbs are human, a first time treatment might result in an antibody response from the female treated with the mAb. Theoretically this may happen because the CDR regions of the mAb, which have never been seen by the immune system of the treated individual before, may be recognized as foreign if presented in a sufficiently large dose. Such a reaction will render the anti-RhD mAb useless in repeated prophylactic treatment.

It is possible that some of these potential problems with mAbs could be overcome by mixing monoclonal antibodies. However, this would mean separate production and purification of an undefined number of antibodies, which will be quite costly. Further, different batch properties of the individual monoclonal antibodies of such a mixture may affect the final product.

DISCLOSURE OF CONTRIBUTION

The present invention provides a method for generating a manufacturing cell line which can express an anti-RhD recombinant polyclonal antibody (anti-RhD rpAb) as a single batch.

DESCRIPTION OF THE INVENTION

The present invention provides methods for the consistent manufacturing of anti-RhD recombinant polyclonal antibody (anti-RhD rpAb). It is contemplated that the present invention will open up the possibility for large-scale manufacturing and production of a new class of prophylactic and therapeutic anti-RhD antibody products.

An anti-RhD rpAb of the present invention potentially has some advantages over monoclonal anti-Rhesus D antibodies. First of all every potential Rhesus D epitope will be covered by more than one antibody, thus an anti-RhD rpAb composition can be used in the prophylactic treatment of both RhD(-) and RhD^{VI} females bearing a RhD(+) child. Hence, it will not be necessary to mix mAb from different production and purification batches in order to obtain full prophylactic effect.

Further, in the instance where mAbs should prove to be immunogenic due to the high concentration of one single or a few molecules, an anti-RhD rpAb may be a good alternative. Since an anti-RhD rpAb according to the present invention is composed of between 5 and 56 variant antibody molecules, their individual concentration will be lower, and if one of the antibodies should be depleted due to immunogenicity, there will be plenty of others to cover the Rhesus D antigen, thus prophylaxis will still be efficient.

The production of an anti-RhD rpAb antibody of the present invention can be performed from a single cell line, as a single batch. The generation of a polyclonal manufacturing cell line for the anti-RhD rpAb production will be demonstrated in the detailed description and by a working example.

Definitions

An "antibiotic resistance gene" is a gene encoding a protein that can overcome the inhibitory or toxic effect that an antibiotic has on a cell ensuring the survival and continued proliferation of cells in the presence of the antibiotic.

The term "antibody" describes a functional component of serum and is often referred to either as a collection of molecules (antibodies or immunoglobulin) or as one molecule (the antibody molecule or immunoglobulin molecule). An antibody molecule is capable of binding to or reacting with a specific antigenic determinant (the antigen or the antigenic epitope), which in turn may lead to induction of immunological effector mechanisms. An individual antibody molecule is usually regarded as monospecific, and a composition of antibody molecules may be monoclonal (i.e., consisting of identical antibody molecules) or polyclonal (i.e., consisting of different antibody molecules reacting with the same or different epitopes on the same antigen or even on distinct, different antigens). Each antibody molecule has a unique structure that enables it to bind specifically to its corresponding antigen, and all

natural antibody molecules have the same overall basic structure of two identical light chains and two identical heavy chains. Antibodies are also known collectively as immunoglobulins. The terms antibody or antibodies as used herein are also intended to include chimeric and single chain antibodies, as well as binding fragments of antibodies, such as Fab, Fab´ or $F(ab)_2$ molecules, Fv fragments or scFv fragments or any other stable fragment, as well as full-length antibody molecules and multimeric forms such as dimeric IgA molecules or pentavalent IgM.

The term "anti-RhD antibody-encoding nucleic acid segment" describes a nucleic acid segment comprising a pair of V_H and V_L genetic elements. The segment may further comprise light chain and/or heavy chain constant region genetic elements, e.g. Kappa or Lambda light chain constant region and/or one or more of the constant region domains CH1, CH2, CH3 or CH4 selected from one of the isotypes IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD and IgE. The preferred isotypes are IgG1 and/or IgG3. The nucleic acid segment may also comprise one or more promoter cassettes, either facilitating bi-directional or uni-directional transcription of the V_H and V_L-encoding sequences. Additional transcriptional or translational elements, such as functional leader sequences directing the gene product to the secretory pathway, poly A signal sequences, UCOE's and/or an IRES may also be present in the segment.

The term "anti-RhD recombinant polyclonal antibody" or "anti-RhD rpAb" describes a composition of recombinantly produced diverse antibody molecules, where the individual members are capable of binding to at least one epitope on the Rhesus D antigen. Preferably, the composition is produced from a single manufacturing cell line. The diversity of the polyclonal antibody is located in the variable regions (V_H and V_L regions), in particular in the CDR1, CDR2 and CDR 3 regions.

The term "bias" is used to denote the phenomenon during recombinant polyclonal antibody production, wherein the composition of an expression library, polyclonal cell line, or polyclonal protein alters over time due to random genetic mutations, differences in proliferation kinetics between individual cells, differences in expression levels between different expression construct sequences, or differences in the cloning efficiency of DNA.

The terms "a distinct member of the anti-RhD rpAb" denotes an individual antibody molecule of the recombinant polyclonal antibody composition, comprising one or more stretches within the variable regions, which are characterized by differences in the amino acid sequence compared to the other individual members of the polyclonal protein. These stretches are in particular located in the CDR1, CDR2 and CDR 3 regions.

As used herein, the term "genome" is not to be taken literally as the normal complement of chromosomes present in a cell, but also extra-chromosomal elements that can be introduced

into and maintained in a cell. Such extra-chromosomal elements can include, but are not limited to, mini-chromosomes, YACs (yeast artificial chromosomes), MACs (mouse artificial chromosomes), or HACs (human artificial chromosomes).

The term "head-to-head promoters" refers to a promoter pair being placed in close proximity so that transcription of two genetic elements driven by the promoters occurs in opposite directions (bi-directional transcription). Construction of such a system is described in details in example 3 of US Patent No. 5,789,208, which is hereby incorporated by reference. A head-to-head promoter can also be constructed with a stuffer composed of irrelevant nucleic acids between the two promoters. Such a stuffer fragment can easily contain more than 500 nucleotides.

The term "hot-spot" as in "hot-spot cell line" refers to a pre-established locus of the genome of the cell that has been selected or generated and characterized for highly efficient transcription of an integrated nucleic acid segment of interest upon integration of the expression vector into that site.

The term "immunoglobulin" commonly is used as a collective designation of the mixture of antibodies found in blood or serum, but may also be used to designate a mixture of antibodies derived from other sources or is used in the term "immunoglobulin molecule".

The term "internal ribosome entry site" or "IRES" describes a structure different from the normal 5' cap-structure on an mRNA. Both structures can be recognized by a ribosome to initiate scanning for an AUG codon to initiate translation. By using one promoter sequence and two initiating AUG's, a first and a second polypeptide sequence can be translated from a single mRNA. Thus, to enable co-translation of a first and a second polynucleotide sequence from a single dicistronic mRNA, the first and second polynucleotide sequence can be transcriptionally fused via a linker sequence including an IRES sequence that enables translation of the polynucleotide sequence downstream of the IRES sequence. In this case, a transcribed dicistronic RNA molecule will be translated from both the capped 5' end and from the internal IRES sequence of the dicistronic RNA molecule to thereby produce both the first and the second polypeptide.

As used herein the term "library" refers to a collection of variant nucleic acid sequences. For example a collection of nucleic acid sequences encoding a diverse population of antibody variable heavy chains and/or variable light chains. Where a member of the variant nucleic acid sequence is comprised of two variant genetic elements, e.g. V_H and V_L, it will often be termed a nucleic acid segment. The collection of variant nucleic acid sequences/segments can either be in the form of a pool of such nucleic acid sequences, or it can be a collection of separate nucleic acid sequences (e.g. one unique sequence in each well of a 96 well plate). A library of the present invention typically have at least 3, 5, 10, 20, 50, 1000, 10^4, 10^5 or 10^6

distinct members. In "library of vectors" the variant nucleic acid sequences/segments have been inserted into a vector. However, the terms library and library of vectors can also be used interchangeably.

The term "a library of anti-RhD antibody expression vectors" refers to a collection of variant anti-RhD antibody-encoding nucleic acid sequences inserted into a vector carrying regulatory elements for transcription of the anti-RhD antibodies. The regulatory elements can either be located in the inserted nucleic acid segments or in the vector framework. Preferably the anti-RhD antibody expression vectors also carry at least one recombinase recognition sequences, e.g. a FRT site, it may also carry two different recombinase recognition sequences such as a FRT and a FRT' site.

The term "a majority of the individual cells" refers to a percentage of the cells such as more than 80%, preferably more than 85%, more preferably 90%, 95%, or even 99% or higher.

The term "mass transfer" or "transfer in-mass" is used to describe the transfer of nucleic acid segments of interest from one population of vectors to another population of vectors and doing so for each nucleic acid segments simultaneously without resorting to isolation of the individual segments of interest. Such populations of vectors can be libraries containing for example variable regions, promoters, leaders or enhancing elements of interest. These sequences can then be moved without prior isolation from for example a phage vector to a mammalian expression vector. Especially for antibody sequences this technique ensures that the linkage between V_H and V_L diversity is not lost while moving libraries from, for example, a selection vector (e.g., a phage display vector) to a mammalian expression vector. Hereby the original pairing of V_H and V_L is retained.

As used herein, the term "operably linked" refers to a segment being linked to another segment when placed into a functional relationship with the other segment. For example, DNA encoding a signal sequence is operably linked to DNA encoding a polypeptide if it is expressed as a leader that participates in the transfer of the polypeptide to the endoplasmic reticulum. Also, a promoter or enhancer is operably linked to a coding sequence if it stimulates the transcription of the sequence.

The term "polyclonal antibody" describes a composition of different (diverse) antibody molecules which is capable of binding to or reacting with several different specific antigenic determinants on the same or on different antigens. Usually, the variability of a polyclonal antibody is located in the so-called variable regions of the polyclonal antibody, in particular in the CDR regions. When stating that a member of a polyclonal antibody binds to an antigen, it is herein meant a binding having binding constant that is below 1 mM, preferably below 100 nM, even more preferred below 10 nM.

The term "recombinant polyclonal manufacturing cell line" refers to a mixture/population of protein expressing cells that are transfected with a library of variant nucleic acid segments of interest such that the individual cells, which together constitute the recombinant polyclonal manufacturing cell line, each carry only one transcriptionally active copy of a distinct nucleic acid segment of interest, which encodes one member of the recombinant polyclonal antibody of interest, and that each copy is integrated into the same site of the genome of each cell. The cells constituting the recombinant polyclonal manufacturing cell line are selected for their ability to retain the integrated copy of the distinct nucleic acid segment of interest, for example by antibiotic selection. Cells which can constitute such a manufacturing cell line can be for example bacteria, fungi, eukaryotic cells, such as yeast, insect cells or mammalian cells, especially immortal mammalian cell lines such as CHO cells, COS cells, BHK cells, myeloma cells (e.g., Sp2/0 cells, NS0), NIH 3T3, YB2/0 and immortalized human cells, such as HeLa cells, HEK 293 cells, or PER.C6.

The term "recombinant antibody" is used to describe an antibody molecule or several molecules that is/are expressed from a cell or cell line transfected with an expression vector comprising the coding sequence of the protein which is not naturally associated with the cell. If the antibody molecules are diverse or different, the term "recombinant polyclonal antibody" applies in accordance with the definition of a polyclonal antibody.

The term "recombinase" refers to an enzyme that catalyses recombination between two or more recombination sites or recombination recognition sequences. Recombinases useful in the present invention catalyze recombination at specific recombination sites that are specific nucleic acid sequences recognized by a particular recombinase.

The terms "recombinase recognition site" or "recombination site" describe a nucleic acid sequence which serves as site for both recognition and recombination by a site-specific recombinase enzyme. A recombinase recognition site is generally comprised of short inverted repeat elements (11-13 bp in length) that flank a core sequence (6-8 bp in length). Recombinase recognition sites are also termed recombinase target sites, recombination sites or integration sites and include as examples the FLP-site, loxP-site, attP/attB-sites, six-site, gix-site, R-site and Res-site. Recombinase recognition sites between which a recombinase can catalyze an integration, excision or inversion event are termed matching recombinase recognition sites, for example are two wild type FRT sites considered to match, as well as an attB site and an attP site constitute a matching pair of recombinase recognition sites, whereas, a wildtype FRT site and a mutant FRT site will not necessarily constitute a matching pair of recombinase recognition sites; this will depend on the mutation. These terms are also used interchangeably with the term integration site.

The term "RFLP analysis" refers to "restriction fragment length polymorphism analysis", a method whereby the migratory gel pattern of nucleic acid molecule fragments is analyzed after cleavage with restriction enzymes.

The term "scrambling" describes situations where two or more distinct members of a polyclonal protein, where each member is comprised of two different polypeptide chains, e.g. V_H and V_L chains, is expressed from an individual cell. This situation may arise when the individual cell has integrated into the genome, more than one pair of genetic elements, where each pair of genetic elements encodes a distinct member of the polyclonal protein. In such situations unintended combinations of the polypeptide chains expressed from the genetic elements can be made. "V_H-V_L chain scrambling" is an example of the scrambling defined above. The scrambling occurs when unintended combinations of V_H and V_L polypeptides are produced from a cell where two different V_H and V_L-encoding nucleic acid segments are integrated into transcriptional active sites in the same cell. Such a scrambled antibody molecule is not likely to retain the original specificity, and thus might not have any therapeutic effect.

The term "selection" is used to describe a method where cells have acquired a certain characteristic that enable the isolation from cells that have not acquired that characteristic. Such characteristics can be resistance to a cytotoxic agent or production of an essential nutrient, enzyme, or color.

The terms "selectable marker gene", "selection marker gene", "selection gene" and "marker gene" are used to describe a gene encoding a selectable marker (e.g., a gene conferring resistance against some cytotoxic drug such as certain antibiotics, a gene capable of producing an essential nutrient which can be depleted from the growth medium, a gene encoding an enzyme producing analyzable metabolites or a gene encoding a colored protein which for example can be sorted by FACS) which is co-introduced into the cells together with the gene(s) of interest.

The term "transfection" is herein used as a broad term for introducing foreign DNA into a cell. The term is also meant to cover other functional equivalent methods for introducing foreign DNA into a cell, such as e.g., transformation, infection, transduction or fusion of a donor cell and an acceptor cell.

As used herein, the term "vector" refers to a nucleic acid molecule into which a nucleic acid sequence can be inserted for transport between different genetic environments and/or for expression in a host cell. A vector capable of integrating into the genome of a host cell at a pre-determined, specific locus in the genome is herein named "a vector for site-specific integration". If the vector carries regulatory elements for transcription of the nucleic acid sequence inserted in the vector (at least a suitable promoter), the vector is herein called "an

expression vector". The term "an isotype-encoding vector" refers to a vector carrying nucleic acid sequences encoding an antibody isotype. In the present specification, "phagemid vector" and "phage vector" are used interchangeably. The terms "plasmid" and "vector" are used interchangeably. The invention is intended to include such other forms of vectors, which serve equivalent functions for example plasmids, phagemids and virus genomes or any nucleic acid molecules capable of directing the production of a desired protein in a proper host.

The following style of writing "V_H:LC" and "V_H:V_L" indicate a particular pair of a variable heavy chain sequence with a light chain or a variable light chain sequence. Such particular pairs of V_H and V_L sequences can either be nucleic acid sequences or polypeptides. In the present invention particular V_H and V_L pairs confer binding specificity towards the rhesus D antigen.

Abbreviations: Ab= antibody. Anti-RhD rpAb= anti-Rhesus D recombinant polyclonal antibody. CASY= Cell Counter + Analyzer System. ELISA = Enzyme-Linked Immunosorbent Assay. FRT= Flp Recombinase Target. GFP= Green Flourescent Proteins. HDN= hemolytic disease of the newborn. ITP= idiopathic thrombocytopenic purpura. LTR= Long Terminal Repeat. mAb= monoclonal antibody. pMCB= polyclonal master cell bank. PVDF = polyvinylidene difluorid. pWCB= polyclonal working cell bank. RBC=red blood cells. RhD= Rhesus D. RhD(-)= Rhesus D negative. RhD(+)= Rhesus D positive. RhD^{VI}= Rhesus D category VI antigen. Anti-D=polyclonal immunoglobulin preparation against RhD from hyperimmune donors. SV40 poly A= Simian Virus 40 poly A signal sequence. UCOE= ubiquitous chromatin opening elements. 5′ UTR=5′ untranslated region of the mRNA.

DESCRIPTION OF THE DRAWINGS

Fig. 1A: Flow chart outlining the generation of a recombinant polyclonal manufacturing cell line and the production of a recombinant polyclonal antibody. 1) Illustrates a bulk transfection strategy; 2) illustrates a semi-bulk transfection strategy and 3) illustrates an individual transfection strategy. A) Illustrates the library of anti-RhD antibody expression vectors (horizontal lines), the arrowheads illustrate the grouping of the vectors. In strategy 1 the vectors are grouped in bulk, in strategy 2 they are grouped in smaller fractions (semi-bulk), whereas in strategy 3 they are kept separate from each other (individual). B) Illustrates the transfection, where the number of tubes depends on the grouping of the vectors constituting the library. C) Illustrates selection of cells that site-specifically have integrated an anti-RhD antibody-encoding nucleic acid segment into the host cell genome, D) Illustrates the generation of a polyclonal anti-RhD antibody library stock, where the selected cells constituting the integrated anti-RhD antibody-encoding nucleic acid segments are stored in a freezer. It is optional to bank individual clones or pool the clones. E) Illustrates the beginning of the manufacturing phase, where clones from the stock are thawed (either

individually, from smaller fractions or from a pool). F) Illustrates the stage in the production where the polyclonal cell line is propagated for seeding of a larger bioreactor (intermediate seeding steps are an option although not illustrated). In strategy 2 and 3, this is the stage where the polyclonal cell clone stock no longer is kept as individual clones or semi-bulk fractions, but pooled into a collection of cells, forming a recombinant polyclonal manufacturing cell line (this polyclonal manufacturing cell line may also be stored as a frozen stock). G) Illustrates the final production obtained from the bioreactor manufacturing. Following the production phase, the polyclonal protein composition is harvested for purification and characterization of the product.

Fig. 1B: Flow chart outlining the generation a pWCB/pMCB and a sub-pWCB from individually transfected host cells and the seeding of a polyclonal manufacturing cell line. A) Illustrates a library comprised of variable region-encoding nucleic acid segments, the arrowheads illustrate the individual members of the library. B) Illustrates the transfection, where each individual member of the library is used to transfect a host cell. The transfection requires as many separate tubes as there are individual members of the library. C) Illustrates selection of cells that have integrated a variable region-encoding nucleic acid segment into their genome in a stable manner, D) Illustrates the selection of individual cell lines that have similar proliferation rates and/or productivity, e.g. by cloning and analysis of single cells sorted by FACS. This step is optional in the generation of a pWCB/pMCB and may also be performed after step E. E) Illustrates the generation of a frozen library stock, constituted of n times individual cell lines each expressing one member of the library comprised of variable region-encoding nucleic acid segments used for transfection. It is optional to bank individual clones into a frozen library stock prior to the generation of a pWCB/pMCB. F) Illustrates the mixing of the individual cell lines, where ampoules from the individual library stock are thawed and expanded in separate cell cultures, followed by the mixing of a predefined number of cells from each culture into a single cell culture. G) Illustrates generation of a pWCB/pMCB by freezing down aliquots from the mixed cell culture in F, thereby generating a collection of vials. H) Illustrates the generation of a sub-pWCB by expanding a single vial from the pMCB and freezing down aliquots with approximately the same number of cells as in the vial from the pMCB. I) Illustrates the generation of a polyclonal manufacturing cell line from a seed train (intermediate seeding steps which are not illustrated) initiated either from the pWCB or the sub-pWCB.

Fig. 2: Phage display vector: Em351, an *E. coli* vector used to generate an anti-RhD Fab phage display library by inserting heavy chain variable region and the light chain fragments amplified from a suitable donor into the vector at the indicated AscI/XhoI and NheI/NotI restriction sites, respectively. The vector comprises the following elements: pro Amp and Amp= promoter and ampicillin resistance gene. pUC Ori=origin of replication. Human CH1=sequence encoding human immunoglobulin gamma 1 heavy chain domain 1. Stuffer =

irrelevant sequence inserts which are cut out during insertion of the heavy and light chain fragments. p tac and p lac Z = bacterial promoters. PelB= modified bacterial PelB leaders for targeting expression of the Fab to the periplasmic space of the *E.coli*. Mycut=proteinase recognition site. Amber stop= amber stop codon. gIII= phage M13 truncated geneIII (from bp 198 to the C-terminal).

Fig. 3A-C: Alignment of the nucleic acid sequences encoding the variable heavy chain (V_H) of the 56 selected RhD clones. The individual clone names are indicated to the right of the alignment, and the position of CDR regions are indicated above the alignments.

Fig. 4A-E: Alignment of the nucleic acid sequences encoding the entire light chain of the 56 selected RhD clones. The individual clone names together with an indication of whether it is a Kappa or Lambda chain are indicated to the right of the alignment, and the position of CDR regions are indicated above the alignments.

Fig. 5: Alignment of the amino acid sequences corresponding to V_H of the 56 selected RhD clones. The individual clone names are indicated to the right of the alignment, and the position of CDR regions are indicated above the alignments.

Fig. 6A-B: Alignment of the amino acid sequences corresponding to V_L of the 56 selected RhD clones, wherein (A) corresponds to the Kappa chains and (B) to the Lambda chains. The individual clone names are indicated to the right of the alignment, and the position of CDR regions are indicated above the alignments.

Fig. 7: Neo exp. vector: Schematic representation of the mammalian expression vector used to facilitate site-specific integration into the genome of a host cell of the anti-RhD antibody-encoding nucleic acid segments. The vector comprises the following elements: pro amp and AMP= promoter and ampicillin resistance gene. pUC origin= pUC origin of replication. Restriction enzyme sites: XhoI, AscI, NheI and NotI. P1/P2= promoter set driving the expression of the light chain and IgG heavy chain, respectively. LH= heavy chain leader sequence. VH= Sequence coding for the variable heavy chain of an anti-RhD Ab. Human IgG1 constant heavy= Sequences coding for the human constant IgG1 heavy chain. RBG polyA= Rabbit β-globin polyA signal sequence. BGH polyA= Bovine Growth Hormone polyA signal sequence. LK= kappa chain leader sequence. Light chain= Sequence coding for the light chain of an anti-RhD Ab. FRT site= Flp recombinase recognition sequence. Neomycin= Neomycin resistance gene. SV40 polyA= Simian virus 40 polyA signal sequence.

Fig. 8: Cation exchange chromatograms of anti-RhD rpAb composition from aliquots 3948 and 3949 after 9 weeks cultivation. The lower diagram corresponds to aliquot 3949 and the upper one to aliquot 3948. The Y-axis of the top diagram has been displaced in order to

separate it from the lower diagram. Peaks A – J comprise antibodies differing in net charge and individual antibodies appearing charge heterogeneous.

Fig. 9: Gel picture showing *HinfI* RFLP analysis on RT-PCR product derived from polyclonal cell line aliquots 3948+ and 3949+ (FCW065) producing anti-RhD rpAb after 11 weeks cultivation. Bands which can be assigned to specific clones are identified.

Fig. 10: T-RFLP patterns of anti-Rhesus D antibody light chains from a polyclonal cell culture expressing anti-RhD rpAb with eight different anti-Rhesus D antibodies. The eight different anti-Rhesus D clones have been assigned to the peaks indicated by arrows.

Fig. 11: T-RFLP patterns of anti-Rhesus D antibody heavy chain variable regions from a polyclonal cell culture expressing anti-RhD rpAb with twenty-five different anti-Rhesus D antibodies at a given time point. The twenty-five different anti-Rhesus D clones have been assigned to the peaks indicated by arrows.

Fig. 12: cDNA distribution estimated by T-RFLP of eight different anti-Rhesus D heavy chain-encoding sequences from a polyclonal cell culture which was cultivated for five weeks.

Fig. 13: Shows the relative content (%) of an anti-RhD rpAb with eight different antibodies analyzed using cation-exchange chromatography. Integrated chromatographic peaks were assigned to individual antibodies from the retention times and peak patterns obtained from single antibodies analyzed individually using cation-exchange chromatography under identical conditions.

Fig. 14: Cation-exchange chromatogram of an anti-RhD rpAb with twenty-five individual members from a sample obtained after 4 weeks cultivation. Peaks AC1 to 25 comprise antibodies differing in net charge and individual antibodies appearing charge heterogeneous.

Fig 15: (A) Shows a comparison of the potency of three batches, Sym04:21, Sym04:23, and Sym04:24, of anti-RhD pAb with 25 individual members, produced by fed batch cultivation in 5 L scale. Binding of pAb to RhD-positive erythrocytes was measured by FACS and the mean fluorescence intensity (MFI) is shown as a function of pAb concentration in ng/ml. Further, the functional activity of an anti-RhD pAb with 25 individual members was measured on Sym04:21 and Sym04:24 in a combined ADCC/phagocytosis assay. (B) Shows the ADCC results as percentage of specific lysis of RhD-positive and RhD-negative erythrocytes as a function of pAb concentration in ng/ml. (c) Shows the percentage of phagocytosis of RhD-positive and RhD-negative erythrocytes as a function of pAb concentration in ng/ml.

Fig. 16: Cation-exchange chromatography profiles showing samples taken at different stages during down-stream processing of an anti-RhD rpAb sample containing 25 individual

members represented by material collected following capture elution (A), Sephadex G-25 (B), DEAE-Sepharose (C), and MEP Hypercel (D)

DETAILED DESCRIPTION OF THE INVENTION

The recombinant polyclonal protein expression system

The present invention provides a recombinant polyclonal antibody expression system for the consistent manufacturing of anti-RhD recombinant polyclonal antibody (anti-RhD rpAb) from one or a few cell lines.

One of the major advantages of the manufacturing method of the present invention is that all the members constituting the anti-RhD rpAb can be produced in one or a few bioreactors or equivalents thereof. Further, the anti-RhD rpAb composition can be purified from the reactor as a single preparation without having to separate the individual members constituting the anti-RhD rpAb during the process. In contrast, if one wanted to mimic an anti-RhD rpAb composition by mixing purified anti-RhD monoclonal antibodies (anti-RhD mAbs) (as for example proposed in WO 97/49809) it would require the separate manufacturing in a bioreactor, of each anti-RhD mAb to be included in the composition and most likely the antibodies would be purified individually as well. Such a production of an anti-RhD mAb mixture would be very costly, and time and space consuming compared to the method of the present invention for producing an anti-RhD recombinant polyclonal. Thus, the method as described in WO 97/49809 would naturally result in a practical limit to the number of anti-RhD mAbs that could be included in such a mixture, whereas the technology as described herein generally can produce a polyclonal antibody with as many individual members as desired. Further, the individual members of an anti-RhD rpAb of the present invention are produced under exact same conditions (in the same manufacturing reactor), thus uniform posttranslational modifications are ensured compared to a mixture of anti-RhD mAbs where slight production differences from batch to batch may change the product properties.

In order to obtain a recombinant polyclonal manufacturing cell line which is capable of expressing anti-RhD rpAb without significant loss of the diversity characterizing the polyclonality during the production period, the individual cells within the mixture of cells composing the polyclonal manufacturing cell line will need to be as uniform as possible.

Conventional monoclonal antibody expression techniques using random integration are undesirable for the production of a recombinant polyclonal antibody, since the random nature of the process will cause the number and positions of the integrated nucleic acid sequences to vary from cell to cell. Thus, if recombinant polyclonal antibody is produced by such traditional protocols, it is likely to result in a heterogeneous cell culture with variable expression rates of individual members of the polyclonal protein, and genetic instability due

to positional effects of the integrated nucleic acid segment. This will most likely result in a biased expression of the members constituting the polyclonal protein.

Introduction of the anti-RhD antibody-encoding nucleic acid segment into a predefined genomic site is therefore desirable, this can in principle be achieved by homologous recombination. However, owing to the dominance of illegitimate recombination events, homologous recombination is very inefficient and may also result in introduction of several copies of variant anti-RhD antibody-encoding nucleic acid segments into the genome of a single cell.

To circumvent these problems the expression system of the present invention uses site-specific integration into the genome of the individual host cells. The system of the present invention encompasses a library of anti-RhD antibody expression vectors for site-specific integration comprising the variant nucleic acid segments encoding the anti-RhD rpAb. Individual nucleic acid segments from the library are inserted into individual cells at the same pre-established chromosomal location by site-specific integration at a predefined recombination recognition site or by a recombinase-mediated cassette exchange procedure, thereby generating a cell line, wherein the individual cells expresses a distinct member of the anti-RhD rpAb. As described below, multiple integrations might occur in some of the cells constituting the recombinant polyclonal manufacturing cell line. This, however, is not considered to pose a problem as long as a majority of the individual cells express a single distinct member of the anti-RhD rpAb. Preferably this is achieved by ensuring a single integrant in the genome of the majority of the individual cells or if there are more integrants, ensuring that only one is transcribed.

Recombinases such as Cre, Flp, beta-recombinase, Gin, Pin, PinB, PinD, R/RS, Tn3 resolvase, XerC/D integrase/recombinase, lambda integrase, or phage ΦC31 integrase can be used. Suitable recombinases for integration into the chromosomal location can be provided either (i) by expression from the cell's own genome into which said nucleic acid segment is introduced, (ii) by being operatively encoded by the vector inserted into the cell, (iii) through expression from a second nucleic acid molecule, or (iv) as a protein. In a preferred embodiment, the anti-RhD antibody-encoding nucleic acid segment contained in an individual vector of the library is integrated into a locus that mediates high-level transcription and expression of the anti-RhD antibody nucleic acid segment, a so-called "hot-spot".

The host cell line used is preferably a mammalian cell line comprising those typically used for biopharmaceutical protein expression, e.g., CHO cells, COS cells, BHK cells, myeloma cells (e.g., Sp2/0 cells, NS0), YB2/0, NIH 3T3, and immortalized human cells, such as HeLa cells, HEK 293 cells, or PER.C6. In the present invention CHO cells were used. However, a person of ordinary skill in the art would easily be able to substitute CHO cells with other mammalian cells as described, or even utilize other types of cells, including plant cells, yeast cells, insect

cells, fungi and bacteria. Thus, the choice of cell type is not intended to be limiting to the invention. In a preferred embodiment, a mammalian cell line containing a pre-characterized hot-spot, mediating high expression levels of the anti-RhD rpAb is used for the manufacture. In an even more preferred embodiment, the mammalian cell line contains a single recombinase recognition site located in a pre-identified hot-spot.

In a further embodiment of the present invention, variant anti-RhD antibody-encoding nucleic acid segments are integrated in a site-specific manner utilizing the same chromosomal integration site in the host cells. Such incorporation into a single specific site minimizes positional effects otherwise seen with random integration or integration into multiple sites in a genome. Further, scrambling among V_H and V_L chains is not likely to occur when using a single specific site for integration.

In a host cell line comprising a site-specific integration system, the individual transfected host cells are expressing the same overall antibody apart from the differences observed in the variable region of the antibody. Therefore, a majority of cells within such a pool of cells should display similar characteristics with respect to productivity and genetic stability and hence this technology offers the possibility of a controlled production of an anti-RhD rpAb.

In addition to the variability of the V_H and V_L regions, in particular the CDR regions, the constant regions may also be varied with respect to isotype. This implies that one particular V_H and V_L pair may be produced with varying constant heavy chain isotypes, e.g. the human IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD and IgE. Thus, an anti-RhD rpAb may comprise antibody molecules that are characterized by sequence differences between the individual antibody molecules in the variable region (V region) as well as in the constant region. The anti-RhD rpAb composition can be composed of antibodies with any heavy chain isotype mentioned above or combinations thereof. Preferred anti-RhD rpAb compositions contain IgG1 constant regions, IgG3 constant regions or IgG1 and IgG3 constant regions. In a preferred embodiment of the present invention each or some of the V_H and V_L pairs are expressed with a human IgG1, IgG3, IgA1 and/or IgA2 constant heavy chain.

In order to provide a library of anti-RhD antibody-encoding nucleic acid segments a number of methods known in the art may be utilized. A first library comprising V_H and V_L-encoding segments may either be generated by combinatorial techniques (e.g. EP 0 368 684) or techniques maintaining the cognate pairing (pairs of variable region-encoding sequences derived from the same cell, described in WO 05/042774 claiming the priority of the unpublished patent application DK 200400782). Further, V_H and V_L-encoding segment libraries may be generated by incorporating isolated CDR gene fragments, into an appropriate framework (e.g. Soderlind, E. et al., 2000. Nat. Biotechnol. 18, 852-856), or by mutation of one or more anti-RhD V_H and V_L-encoding sequences. This first library is screened for V_H and V_L -encoding nucleic acid segments producing antibodies or fragments

with binding specificity towards RhD, thereby generating a library of anti-RhD Ab-encoding nucleic acid segments. In particular with combinatorial libraries the screening is preceded by an enrichment step for example a so-called biopanning step.Known biopanning technologies are phage display (Kang, A.S. et al. 1991. Proc Natl Acad Sci U S A 88, 4363-4366), ribosome display (Schaffitzel, C. et al. 1999. J. Immunol. Methods 231, 119-135), DNA display (Cull, M.G. et al. 1992. Proc Natl Acad Sci U S A 89, 1865-1869), RNA-peptide display (Roberts,R.W., Szostak,J.W., 1997. Proc Natl Acad Sci U S A 94, 12297-12302), covalent display (WO 98/37186), bacterial surface display (Fuchs, P. et al. 1991. Biotechnology 9, 1369-1372), yeast surface display (Boder, E.T., Wittrup, K.D., 1997. Nat Biotechnol 15, 553-557) and eukaryotic virus display (Grabherr,R., Ernst,W., 2001. Comb. Chem. High Throughput. Screen. 4, 185-192). FACS and magnetic bead sorting are also applicable for enrichment (panning) purposes using labeled antigen. The screening for Rhesus D binders are generally performed with immunodetection assays such as agglutination, FACS, ELISA, FLISA and/or immunodot assays.

Following screening, the generated sub-library of V_H and V_L-encoding nucleic acid segments, generally needs to be transferred from the screening vector to an expression vectors suitable for site-specific integration and expression in the desired host cell. It is important that the sequences encoding the individual V_H:V_L pairs are maintained during the transfer. This can either be achieved by having the individual members of the sub-library separate and moving V_H and V_L-encoding sequences one by one. Alternatively, the vectors constituting the sub-library are pooled, and the sequences encoding the V_H:V_L pairs are moved as segments, keeping the V_H and V_L-encoding sequences together during the transfer. This process is also termed mass transfer, and enables an easy transfer of all the selected V_H:V_L pairs from one vector to another.

In a further embodiment of the present invention, an anti-RhD recombinant polyclonal antibody composition comprises a defined subset of individual antibodies, based on the common feature that they exhibit binding to at least one epitope on the Rhesus D antigen e.g. epD1, epD2, epD3, epD4, epD5, epD6/7, epD8 and/or epD9, but not or very weakly to Rhesus C, c, E, e antigens. Preferably the anti-RhD rpAb composition is composed of at least one antibody which bind to epD3, epD4 and epD9 (RhD category VI antigen binding antibody) and further antibodies which at least in combination binds to the remaining epitopes epD1, epD2, epD5, epD6/7 and epD8, e.g. an antibody against RhD category II or III antigen, or a RhD category IV or V antigen binding antibody combined with an antibody against category VII antigen. Typically an anti-RhD rpAb composition has at least 5, 10, 20, 50, 100 or 500 distinct variant members. The preferred number of variant members range between 5 and 100, even more preferred between 5 and 50 and most preferred between 10 and 25.

A further embodiment of the present invention is a recombinant polyclonal manufacturing cell line, comprising a collection of cells transfected with a library of anti-RhD polyclonal antibody-encoding nucleic acid segments, wherein each cell in the collection is capable of expressing one member of the library, which encodes a distinct member of an anti-RhD rpAb or fragment and which is located at the same site in the genome of individual cells in said collection, wherein said nucleic acid segment is not naturally associated with said cell in the collection.

In an additional embodiment the variant nucleic acid segments encoding the anti-RhD rpAb are all derived from naturally occurring sequences, for example isolated from a donor, either as combinatorial V_H:V_L pairs or as cognate pairs, and not derived by mutation.

Compositions of cells that contain variant nucleic acids located at a single specific site in the genome within each cell have been described in WO 02/44361. This document discloses the use of the cells to identify molecules having desirable properties, but the reference does not deal with the provision of a production system or with the provision of polyclonal antibody characterized by a specific binding to an antigen.

The host cell

A suitable host cell comprises, in a region of its genome, one or more suitable recombination sites, i.e., nucleic acid sequences recognizable by one or more recombinase enzymes, hence also termed recombinase recognition sequences. To be able to select for integrants, (i.e., cells having an integrated copy of an anti-RhD antibody-encoding nucleic acid segment in an integration site) the recombination site is operably linked to a first selection gene (e.g., an antibiotic resistance gene) situated 3' (downstream) to the recombination site. Furthermore, a weak promoter (e.g., a truncated SV40 early promoter) and a transcription start codon may be situated 5' (upstream) to the recombination site that constitutes an integral part of the resistance marker-coding region. Thus, the transcription start codon initiates the start of transcription of the selection gene in the host cell before transfection with the library of anti-RhD antibody expression vectors encoding the anti-RhD rpAb. Preferably, the host cell line only has one recombination site, and if it has more than one recombinase recognition sequence, these should be non-homologous as described in the section "*The vector for site-specific integration*", and only allow for a single integration into the genome.

Host cells for site-specific integration as described above can be generated from any cell which can integrate DNA into their chromosomes or retain extra-chromosomal elements such as mini-chromosomes, YACs (Yeast artificial chromosomes), MACs (Mouse artificial chromosomes), or HACs (Human artificial chromosomes). MACs and HACs are described in detail in WO 97/40183, hereby incorporated by reference. Preferably mammalian cells such as CHO cells, COS cells, BHK cells, myeloma cells (e.g., Sp2/0 or NS0 cells), fibroblasts such

as NIH 3T3, and immortalized human cells, such as HeLa cells, HEK 293 cells, or PER.C6, are used. However, non-mammalian eukaryotic or prokaryotic cells, such as plant cells, insect cells, yeast cells, fungi, E. coli etc., can also be employed.

In one embodiment of the present invention, the cell line which is to be used as starting material is sub-cloned by performing a so-called limiting dilution of the cell line down to a single cell level, followed by growing each single cell to a new population of cells prior to transfection with the library of vectors of interest. Such sub-cloning can also be performed later in the process of selecting the right cell line, if desired.

The host cells for site-specific integration may be obtained by transfection with a randomly integrating plasmid comprising a weak promoter (e.g., a truncated SV40 early promoter), a transcription start codon, a recombination site situated 3' to the start codon. Preferably, the integrating plasmid also comprises a marker gene coupled to a first selection gene. One example of such an integrating plasmid is the pFRT/LacZeo2 from Invitrogen (Carlsbad, CA). The marker gene can be used to evaluate the relative strength of expression at the genomic location used for inserting a nucleic acid sequence of interest. A marker gene, (e.g., beta-galactosidase (LacZ), green fluorescent protein (GFP) or a cell surface marker) can be linked to the first selection gene in a gene fusion or transcriptionally linked by an IRES (internal ribosomal entry site) such that co-expression of the first selection gene and marker gene occurs. The use of a selection gene that establishes a survival pressure on the cells (e.g. drug resistance or nutritional depletion) combined with a marker allowing for evaluation of the relative expression levels from cell line to cell line is an efficient method to ensure high producing cells which maintain the integrated plasmid within the genome. Cells with the recombination sequence inserted at a spot with particularly active transcription will lead to high expression of the marker gene e.g. GFP or LacZ. High expressers can be selected by fluorescence activated cell sorting (FACS) and cloned. At this point it should also be analyzed whether the integrant is a single integrant. This can be performed by real-time PCR and Southern blotting. The preparation of cells having an FRT site at a pre-determined location in the genome was described in e.g. US 5,677,177.

Another method for evaluating relative expression levels from cells transfected with an integrating plasmid is to perform an additional integration-excision step on the cells generated as described above. This pool of selected cells are transfected again, with a plasmid encoding a recombinase corresponding to the recombination site of the integrating plasmid and a second plasmid containing a second selection marker without a start codon, the coding region of which is preceded by a recombination sequence likewise corresponding to the first integrating plasmid. This second plasmid also contains the coding sequence for a fluorescent marker protein (e.g., GFP (or equivalent fluorescent proteins) driven by a suitable promoter. The recombinase mediates integration of this plasmid into the host cell genome

where a similar recombination sequence previously has been inserted by the integrating plasmid. Cells with the recombination sequence inserted at a spot with particularly active transcription will lead to high expression of the fluorescent protein. High expressers are selected by fluorescence activated cell sorting (FACS) and cloned. Clones with consistently high expression and containing one copy of the inserted plasmid are transfected with the recombinase and selected by the first selection marker, identifying cells where the second plasmid sequence has been removed by the recombinase, making the first selection marker work again. These cells still contain the first recombination sequence inserted at a transcriptional hot-spot and can now be used for the expression of genes of interest.

Cell lines, which achieve high expression of the marker gene upon integration of a single copy of the plasmid, are used for transfection with the anti-RhD antibody expression library. The recombination site in the host cell is preferably located in a gene or region of particularly active expression, i.e., in a so-called hot-spot.

The vector for site-specific integration

A suitable vector comprises a suitable recombination site linked to a suitable selection gene different from the selection gene used for construction of the host cell. Suitable selection genes for use in mammalian cell expression include, but are not limited to, genes enabling for nutritional selection, such as the thymidine kinase gene (TK), glutamine synthetase gene (GS), tryptophan synthase gene (trpB) or histidinol dehydrogenase gene (hisD). Further, selection markers are antimetabolite resistance genes conferring drug resistance, such as the dihydrofolate reductase gene (dhfr) which can be selected for with hypoxanthine and thymidine deficient medium and further selected for with methotrexate, the xanthine-guanine phosphoribosyltransferase gene (gpt), which can be selected for with mycophenolic acid, the neomycin phosphotransferase gene (neo) which can be selected for with G418 in eukaryotic cells and neomycin or kanamycin in prokaryotic cells, the hygromycin B phosphotransferase (hyg, hph, hpt) gene which can be selected for with hygromycin, the puromycin N-acetyl-transferase gene (pac) which can be selected for with puromycin or the Blasticidin S deaminase gene(Bsd) which can be selected for with blasticidin. Finally, genes encoding proteins that enables sorting e.g. by flow cytometry can also be used as selection markers, such as green fluorescent protein (GFP), the nerve growth factor receptor (NGFR) or other membrane proteins, or beta-galactosidase (LacZ).

In one aspect of the present invention, the selectable gene is neither preceded by a promoter nor equipped with a translation initiating codon. The promoter and ATG codon is provided at the selected site-specific recombination site. If the vector is integrated at a location other than the selected recombination site in the genome of the host cell, no expression of this second selection gene can occur due to lack of promoter and initiation codon. If integration

occurs at the selected recombination site in the genome of the host cell, the second selection gene is expressed and expression of the first selection gene is lost.

Integration may e.g., be carried out using a so-called FRT site/Flp recombinase recognition sequence (5´-gaagttcctattccgaagttcctattctctagaaagtataggaacttc-3´ (SEQ ID NO 1) or variants thereof) in the genome and on the vector for site-specific integration together with the Flp recombinase or mutants thereof from Saccharomyces cerevisiae. However, other recombinase systems may equally well be used, including those of Cre recombinase and a variety of lox sites such as loxP from bacteriophage P1 or variants or mutants thereof, e.g., lox66, lox71, lox76, lox75, lox43, lox44 and lox511 (C. Gorman and C. Bullock, Curr. Opinion in Biotechnology 2000, 11: 455-460) or by using phage integrase ΦC31 or lambda integrase, which carries out recombination between the attP site and the attB site (A.C. Groth et al. PNAS 2000, 97: 5995-6000). Further recombinase systems that could be utilized in the present invention are, but are not limited to, the β-recombinase-six system from bacterial plasmid pSM19035 (Rojo and Alonso 1995), the Gin-gix system from bacteriophage Mu (Crisona et al 1994), the R-RS system from Zygosaccharomyces rouxii (Onouchi et al 1995), or Tn3 resolvase which recognize res recombination sites (Stark et al 1994) or the XerC/D system from E coli (Blakely and Sherratt 1994).

A further variant of the site-specific recombination system, termed recombinase cassette mediated exchange (RMCE),uses non-homologous recombination sites. In such a system, two non-identical recombination sites are introduced into the host genome for the generation of specific target sites. Recombination sites corresponding to those flanking the target site also flank the construct containing the gene of interest. Such a system has been described in WO 99/25854, which is hereby incorporated by reference in its entirety. The use of non-homologous recombination sites was shown to suppress excision of the gene of interest from the chromosome. The non-identical recombination sites can be composed of any of the recombination sites described above as long as the corresponding recombinases are provided and the sites cannot recombine with each other. For example, non-identical recombination sites could consist of a FRT site and a mutant FRT site utilizing a Flp recombinase for integration (Schlake and Bode 1994, Biochemistry 33, 12746-12751), a loxP site and a mutant non-compatible loxP site utilizing the Cre recombinase (Langer et al 2002, Nucleic Acids Res. 30, 3067-3077) or a FRT site and a loxP site utilizing Flp and Cre recombinases for the integration (Lauth et al 2002, Nucleic Acids Res. 30, 21, e115).

Further, a system using two different FRT sites has been described in Verhoeyen et al., Hum. Gene Ther. 2001 12, 933-44. In this approach the integrating plasmid is transferred to the host cells by retroviral infection. The plasmid consists of a combination of a reporter gene and a first selection marker gene as well as the retroviral elements required for infection. The retroviral 3'LTR contains two different FRT sites. A non functional second selection marker

gene, which lacks a promoter and the translation initiating codon is located 3' to these sites. During the process of retroviral infection the 3'LTR sequence is copied to the 5'LTR. This results in the flanking of the reporter gene and the first selection marker gene by two different FRT sites on each side. The sequence between the outer FRT sites can be exchanged against an anti-RhD antibody-encoding nucleic acid segment under the control of a strong promoter. The cassette containing the anti-RhD antibody-encoding nucleic acid segment is flanked by the same set of FRT sites. The reaction is catalyzed by the Flp recombinase. In the transfected exchange plasmid an IRES element and a translation initiating codon are located further downstream of the nucleic acid segment. After replacement of the integrated cassette the non functional selection marker gene located in the 3' LTR sequence outside the FRT sites is activated by the translation initiating codon provided by the cassette constituting the anti-RhD antibody-encoding nucleic acid segment. The exchange status can further be enriched if a negative selection marker (e.g. thymidine kinase) is present in the integrating vector.

The integrating vector can also be transferred to the host cells by standard transfection. In this case the integrating cassette is flanked by an FRT site at the 5' end and a different FRT' site at the 3' end. The ATG-deficient second resistance marker gene is positioned further downstream of the 3' FRT' site. The exchange for an anti-RhD antibody-encoding nucleic acid segment proceeds as described for the retroviral system.

Another system that prevents excision of the anti-RhD antibody-encoding nucleic acid segment after its site-specific integration into the chromosome is the ΦC31 integrase, also mentioned above. This system has been described thoroughly in patent applications WO 01/07572 and WO 02/08409, hereby incorporated by reference in their entirety.

Preferably the integrating vector is an isotype-encoding vector, where the constant regions (preferably including introns) are present in the vector prior to insertion of the V_H and V_L comprising segment from the screening vector. The constant regions present in the vector can either be the entire heavy chain constant region (CH_1 to CH_3 or to CH_4) or the constant region encoding the Fc part of the antibody (CH_2 to CH_3 or to CH_4). The light chain Kappa or Lambda constant region may also be present prior to transfer. The choice of the number of constant regions present, if any, depends on the screening and transfer system used. The heavy chain constant regions can be selected from the isotypes IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD and IgE. Preferred isotypes are IgG1 and/or IgG3.

Further, the vector for site-specific integration of the anti-RhD antibody-encoding nucleic acid segment contains suitable promoters or equivalent sequences directing high levels of expression of each of the V_H and V_L chains. Preferably the promoters are of mammalian origin. The V_H and V_L-encoding sequences are placed as pairs in the vector used for integration (one pair per vector molecule), thereby ensuring that they will be kept together throughout the integration process. Preferably, the promoters are located within the anti-RhD

antibody-encoding nucleic acid segment. For bi-directional expression a head-to-head promoter configuration in the expression vector is used (Fig. 7). For unidirectional expression two promoters, one in front of the V_H genetic element and one in front of the V_L genetic element, or one promoter in front of V_H or V_L combined with an IRES sequence between the heavy and light genetic elements, can be used to achieve expression.

A nucleic acid sequence encoding a functional leader sequence can be included in the expression vector to direct the gene product to the endoplasmic reticulum or a specific location within the cell such as an organelle. A strong polyadenylation signal sequence can be situated 3' of the heavy chain and light chain-encoding sequences. The polyadenylation signal ensures termination and polyadenylation of the nascent RNA transcript and is correlated with message stability.

The expression vector for site-specific integration can carry additional transcriptional regulatory elements, such as enhancers or UCOE (ubiquitous chromatin opening elements) for increased expression at the site of integration. Enhancers are nucleic acid sequences that interact specifically with cellular proteins involved in transcription. The UCOE opens chromatin or maintains chromatin in an open state and facilitates reproducible expression of an operably-linked gene (described in more detail in WO 00/05393, hereby incorporated by reference in its entirety). When one or more of the regulatory elements described in the above are integrated into the chromosome of a host cell they are termed heterologous regulatory elements.

Establishing an expression system for high-level expression of a polyclonal protein

Methods for introducing a nucleic acid sequence into a cell are known in the art. These methods typically include the use of a DNA vector to introduce the sequence of interest into the cell, the genome or an extra-chromosomal element. Transfection of cells may be accomplished by a number of methods known to those skilled in the art, including calcium phosphate precipitation, electroporation, microinjection, liposome fusion, RBC ghost fusion, protoplast fusion, and the like.

For the transfection of a host cell line, a library of anti-RhD antibody expression vectors, wherein each individual vector comprises one single copy of a nucleic acid segment, encoding a distinct member of the anti-RhD rpAb, is used. This library of anti-RhD antibody expression vectors collectively encodes the anti-RhD rpAb. Suitable vectors for site-specific integration were described in the previous section. The individual vectors constituting the library of anti-RhD antibody-encoding nucleic acid segments can either be mixed together into a single composition, or the individual vectors encoding an individual member of the anti-RhD rpAb can be kept in separate compositions or in mixtures of approximately 5 to 50 individual vectors of the library in a composition.

The generation of a recombinant polyclonal manufacturing cell line and the production of a recombinant polyclonal antibody from such a cell line can be obtained by several different transfection and manufacturing strategies. These strategies are outlined in Fig. 1A and described in more detail below.

One way of generating the recombinant polyclonal manufacturing cell line, is to use a library of vectors mixed together into a single composition for the transfection of the host cell line. This method is termed bulk transfection or transfection in bulk (all the individual members of the library are transfected into the host cell line in one tube). Generally, the vector and host cell design previously described will ensure that a polyclonal cell line will be obtained upon appropriate selection. In such a cell line a majority of the individual cells have integrated one copy of a nucleic acid segment, encoding a distinct member of the anti-RhD rpAb from the library of anti-RhD antibody expression vectors into the genome. The single copy of the nucleic acid segment is integrated into a single specific site of the genome of each cell in the collection of cells, thereby generating a polyclonal cell line comprised of individual cells expressing individual members of the anti-RhD rpAb. Preferably a frozen stock of the polyclonal cell line is generated before initiation of the anti-RhD rpAb manufacturing.

Another way of generating the recombinant polyclonal manufacturing cell line is to split the library of anti-RhD antibody expression vectors into fractions, containing approximately 5 to 50 individual vectors of the library before transfection. Preferably, a fraction of the library constitutes 10 to 15 individual vectors. Each composition is then transfected into an aliquot of host cells. This method is termed semi-bulk transfection. The number of aliquots transfected will depend on the size of the library and the number of individual vectors in each fraction. If the library for example constitutes 50 distinct variant members, which are split into fractions containing 10 distinct variant members in a composition, 5 aliquots of host cells would need to be transfected with a library composition constituting a distinct fraction of the original library. The aliquots of host cells are selected for site-specific integration. Preferably, the distinct aliquots are selected separately. However, they can also be pooled before selection. To obtain the desired polyclonal cell line for manufacturing, the aliquots can be mixed before generating the frozen stock, immediately after they have been retrieved from the stock or after a short proliferation time. Optionally, the aliquots of cells are kept separate throughout production, and the polyclonal antibody composition is assembled by combining the products of each aliquot rather than the aliquots of cells before production.

A third way of generating the recombinant polyclonal manufacturing cell line, is a high throughput method in which host cells are transfected separately using the individual vectors constituting the library of anti-RhD antibody expression vectors. This method is termed individual transfection. The individually transfected host cells are preferably selected for site-specific integration separately. However, they can also be pooled before selection. The

individual cell clones generated upon selection may be analyzed with respect to proliferation time and integration pattern and preferably, those with similar growth rates and a single site-specific integrant are used to generate a frozen library stock. The individual cell clones can be mixed to obtain the desired polyclonal cell line before generating the stock, immediately after they have been retrieved from the stock, or after a short proliferation time. Alternatively, the individually transfected host cells are mixed even earlier, namely before selection is performed.

A shared feature in the manufacturing strategies outlined in the above is that all the individual members constituting the anti-RhD rpAb can be produced in one, or a limited number of bioreactors, with approximately 5 to 10 as the maximum. The only difference is the stage at which one chooses to generate the collection of cells that constitutes the recombinant polyclonal manufacturing cell line.

The host cell line to be used for expression and production of an anti-RhD rpAb has at least one nucleic acid sequence recognizable by a recombinase enzyme. The preparation of such a host cell line was described in the section "*The host cell*".

The vector for site-specific integration is preferably integrated in a predefined genomic locus that mediates high-level expression, a so-called hot-spot.

If expression levels need to be increased, gene amplification can be performed using selection for a DHFR gene or a glutamine synthetase (GS) gene. This requires the use of vectors comprising such a selection marker.

The following description is one example of how to obtain a recombinant polyclonal antibody manufacturing cell line, where scrambling of the chains is minimal if existing at all.

Nucleic acid segments containing a universal promoter cassette for constitutive expression having two promoters placed in opposite transcriptional direction, such as a head-to-head construction surrounded by the variable heavy chain and the whole of the kappa light chain is constructed, allowing transfer of the whole construct into a vector for site-specific integration said vector comprising a FRT site and a neomycin resistance gene and the heavy chain constant region. It is contemplated that a promoter cassette for inducible expression can also be used. Furthermore, the promoters can be placed head-to-tail for unidirectional transcription. CHO-Flp-In cells (Invitrogen, Carlsbad, CA) which stably express the lacZ-Zeocin fusion gene, are used for the experiment, rendering the cells resistant to the antibiotic Zeocin. The cells are maintained in a suitable media medium containing Zeocin. The cells are co-transfected in bulk with a plasmid expressing the Flp recombinase and the library of anti-RhD antibody expression vectors for site-specific integration encoding the anti-RhD rpAb and a different selection marker (neomycin). After transfection, the cells are cultivated in the

presence of neomycin. Cells that exhibit resistance to neomycin are then preferably adapted to growth in suspension as well as serum free conditions, this can be performed in one or two steps and with or without selection pressure. Alternatively, the cells are adapted to grow in suspension under serum free conditions prior to transfection of the cells. When the polyclonal cell line has been adapted to the appropriate conditions scaling up can be initiated using different culture systems, such as conventional small culture flasks, Nunc multilayer cell factories, small high yield bioreactors (MiniPerm, INTEGRA-CELLine, wavebags, BelloCell) and spinner flasks to hollow fiber-and bioreactors. The suitable production time and choice of final bioreactor size are dependent on the desired yield of protein from the batch and expression levels from the cell line. Times might vary from a couple of days up to three month. The cells are tested for antibody production using ELISA. The expressed anti-RhD rpAb is isolated from the supernatant. The anti-RhD rpAb is purified and characterized. Examples of purification and characterization procedures are described later.

Clonal Diversity/Polyclonality

One of the characteristics of a polyclonal antibody is that it is constituted of a number of individual antibody molecules where each antibody molecule is homologous to the other molecules of the polyclonal antibody, but also has a variability that is characterized by differences in the amino acid sequence between the individual members of the polyclonal antibody. These differences are normally confined to the variable region in particular the CDR regions, CDR1, CDR2 and CDR3. This variability of a polyclonal antibody can also be described as diversity on the functional level, e.g., different specificity and affinity with respect to different antigenic determinants on the same or different antigens located on one or more targets. In a recombinant polyclonal antibody the diversity constitutes a sub-set of the diversity observed in a donor derived immunoglobulin product. Such a sub-set is carefully selected and characterized with respect to its ability to bind desired target antigens, in this particular case the Rhesus D antigen.

One of the concerns with respect to production of a recombinant polyclonal antibody may be whether the clonal diversity is maintained in the final product. The clonal diversity may be analyzed by RFLP or sequencing of (RT)-PCR products from the cells expressing the anti-RhD rpAb. The diversity can also be analyzed on protein level by functional tests (e.g., ELISA) on the anti-RhD rpAb produced by the cell line, by anti-idiotypic antibodies to individual members or by chromatographic methods.

Clonal bias, if it exists, can be estimated by comparing the clonal diversity of the initial library, used for transfection, with the diversity found in the pool of cells (polyclonal cell line) expressing the anti-RhD rpAb.

Clonal diversity of an anti-RhD rpAb can be assessed as the distribution of individual members of the polyclonal composition. This distribution can be assessed as the total number of different individual members in the final polyclonal antibody composition compared to the number of different encoding sequences originally introduced into the cell line during transfection. In this case sufficient diversity is considered to be acquired when at least 50% of the encoding sequences originally used in the transfection can be identified as different individual members of the final anti-RhD rpAb. Preferably at least 75% of the anti-RhD antibody-encoding sequences used for transfection can be identified as antibodies in the final composition. Even more preferred at least 85% to 95%, and most preferred a 100% of the anti-RhD antibody-encoding sequences used for transfection can be identified as antibodies in the final composition.

The distribution of individual members of the anti-RhD rpAb composition can also be assessed with respect to the mutual distribution among the individual members. In this case sufficient clonal diversity is considered to be acquired if no single member of the composition constitutes more than 75 % of the total number of individual members in the final anti-RhD rpAb composition. Preferably, no individual member exceeds more that 50%, even more preferred 25 % and most preferred 10% of the total number of individual members in the final polyclonal composition. The assessment of clonal diversity based on the distribution of the individual members in the polyclonal composition can be performed by RFLP analysis, sequence analysis or protein analysis such as the approaches described later on for characterization of a polyclonal composition.

Clonal diversity may be reduced as a result of clonal bias which can arise a) during the cloning process, b) as a result of variations in cellular proliferation, or c) through scrambling of multiple integrants. If such biases arise, each of these sources of a loss of clonal diversity is easily remedied by minor modifications to the methods as described herein.

In order to limit bias introduced by cloning of the variable domains into the appropriate vectors, the transfer of the genes of interest from one vector to another may be designed in such a way that cloning bias is limited. Mass transfer techniques and a careful selection of the *E. coli* strain used for amplification can reduce the cloning bias. Another possibility is to perform an individual transfer of each polynucleotide encoding an individual member of the polyclonal antibody, between screening vectors and vectors for site-specific integration.

It is possible that variations in cellular proliferation rates of the individual cells in the cell line could, over a prolonged period of time, introduce a bias into the anti-RhD rpAb expression, increasing or reducing the presence of some members of the anti-RhD rpAb expressed by the cell line. One reason for such variations in proliferation rates could be that the population of cells constituting the starting cell line used for the initial transfection is heterogeneous. It is known that individual cells in a cell line develop differently over a prolonged period of time.

To ensure a more homogeneous starting material, sub-cloning of the cell line prior to transfection with the library of interest may be performed using a limiting dilution of the cell line down to the single cell level and growing each single cell to a new population of cells (so-called cellular sub-cloning by limiting dilution). One or more of these populations of cells are then selected as starting material based on their proliferation and expression properties.

Further, the selection pressure used to ensure that only cells that have received site-specific integrants will survive, might affect proliferation rates of individual cells within a polyclonal cell line. This might be due to the favoring of cells that undergo certain genetic changes in order to adapt to the selection pressure. Thus, the choice of selection marker might also influence proliferation rate-induced bias. If this occurs, different selection markers should be tested. In cases where selection is based on a substance that is toxic to the cells, the optimal concentration should be tested carefully, as well as whether selection is needed throughout the entire production period or only in the initial phase.

An additional approach to ensure a well defined cell population is to use fluorescence activated cell sorting (FACS) after the transfection and selection procedures. Fluorescence labeled antibodies can be used to enrich for highly productive cells derived from a pool of cells transfected with IgG constructs (Brezinsky *et al.* J. 2003. Immunol Methods 277, 141-155). This method can also be used to sort cells expressing similar levels of immunoglobulin, thereby creating a homogenous cell population with respect to productivity. Likewise, by using labeling with the fluorescent dye 5,6-carboxylfluorescein diacetate succinimidyl ester (CFSE) cells showing similar proliferation rates can be selected by FACS methods. Further, differences in expression levels of the individual members of the anti-RhD rpAb may also introduce a bias into the final product over a prolonged period of time.

If the polyclonal cell line is generated by mixing separately transfected clones after selection (the 3rd approach in Fig. 1A), the following selection criteria may be set up for the individual clones at the cell culture level prior to mixing: proliferation rates have to be between 24 and 32 hours, the productivity should exceed 1.5 pg antibody per cell per day, and the culture should show a homogenous cell population assessed by an intra cellular staining method. If desired a more homogenous cell population for each individual clone can be obtained with the surface staining method described by Brezinsky prior to mixing the individual clones by gating on a particular area of the population in connection with the FACS analysis.

Even if a proliferation rate-induced, or productivity-induced bias occurs, the loss or over-representation of individual members might not necessarily be critical, depending on the diversity requirements of the final anti-RhD rpAb product.

In cells with site-specific single integrants, the cells will only differ in the sequence of the variable regions of the antibodies to be expressed. Therefore, the different cellular effects

imposed by variation in integration site and gene regulatory elements are eliminated and the integrated segments have minimal effects on the cellular proliferation rate. Neither scrambling nor multiple integrations is likely to cause problems in the proliferation rate of the manufacturing cell line, since these are rare events. Random integrations generally occur with an efficiency of approximately 10^{-5}, whereas site-specific integration occurs with an efficiency of approximately 10^{-3}. If multiple integrations should unexpectedly pose a problem, an alternative is to repeat the transfection with the library of anti-RhD antibody expression vectors, because the likelihood that the event will reoccur is very small, as described above.

Considering statistics, bulk transfection of a large number of cells also constitutes a way to circumvent an undesired clonal bias. In this approach, a host cell line is transfected in bulk with the library of anti-RhD antibody expression vectors. Such a library constitutes many copies of each distinct member of the library. These copies should preferably be integrated into a large number of host cells. Preferably at least 100, 1000, 10000 or 100000 individual cells are transfected with copies of distinct members of the library of variant nucleic acid segments. Thus, if a library of distinct variant nucleic acid segments is composed of 1000 distinct members which are each integrated into 1000 individual cells, 10^6 clones containing a site-specifically integrated anti-RhD antibody-encoding segment should arise from the transfection. In this manner the gausian curve of individual cell doubling rates should influence the general population only in very small degrees. This will increase the probability of keeping the clonal composition constant, even if a low percentage of the manufacturing cells should exhibit aberrant growth and/or expression properties.

Alternatively the semi-bulk transfection or individual transfection methods previously described may be used.

Establishment of a polyclonal working cell bank (pWCB)

The section "*Establishing an expression system for high-level expression of a polyclonal protein*" describes three alternative ways of establishing a polyclonal manufacturing cell line. The section describes the generation of a frozen library stock which is constituted of a collection of cells, obtained by bulk or semi-bulk transfection, where each individual cell in the library stock is capable of expressing an individual member from a library of anti-RhD antibody expression vectors. Preferably, the clonal diversity requirements already described is fulfilled by the collection of cells, such that essentially all members of the library can be expressed from a frozen library stock ampoule, when thawn and expanded to establish a polyclonal manufacturing cell line. In the bulk transfection and semi-bulk transfection approaches the frozen library stock, can also be considered as a polyclonal working cell bank (pWCB), in that a single vial from the frozen library stock can be thawn and expanded into a polyclonal manufacturing cell line.

Alternatively, in the previously described third approach for the generation of a recombinant polyclonal manufacturing cell line, the frozen library stock is composed of separate cell lines, which have been individually transfected with an individual member of a library of anti-RhD antibody expression vectors. The transfectants are selected for stable expression of the integrated vector-derived nucleic acid segment from their genome. Preferably, the nucleic acid segments are integrated site-specifically into one or more sites in the genome of the transfectants, and even more preferred in a single site of the genome. The transfected cells obtained e.g. from clonal colonies upon selection may either be isolated and maintained as single clones or pooled to generate a pool of clones expressing the same anti-RhD antibody. In the present invention a single clone of cells as well as pool of clones expressing the same antibody is termed an individual cell line. Thus, if the library of anti-RhD antibody expression vectors constituted 25 individual members, the frozen library stock, in this third approach, would be composed of 25 individual cell lines (not a mixture of cell lines) each expressing an individual member from the library of anti-RhD antibody expression vectors. Hence, one vial from this library stock will result in the generation of a monoclonal anti-RhD antibody if used for manufacturing.

The present invention exemplifies a library of anti-RhD antibody expression vectors. However, the generation of a frozen library stock is independent of the antigen specificity of the polyclonal protein produced from a library comprised of variable region-encoding nucleic acid segments and may be used with any other library comprised of antibody V_H and V_L-encoding nucleic acid segments, or T cell receptor (TcR) α and β-, or γ and δ-encoding nucleic acid segments. A library comprised of variable region-encoding nucleic acid segments can in addition to the variable regions also encode one or more constant regions. Thus, a library comprised of antibody V_H and V_L-encoding nucleic acid segments may result in Fv, scFv, Fab molecules or full-length antibody molecules, and a library comprised of TcR variable region-encoding segments may result in molecules composed of TcR variable domain fragments, soluble TcRs or full-length TcRs.

In situations where the frozen library stock is composed of individual cell lines it will be appropriate to generate a pWCB which can be used for the establishment of the polyclonal manufacturing cell line by thawing and expanding the contents of a single ampoule. The individual cell lines used to generate such a pWCB are either obtained from i) a single clone or ii) a pool of clones (a pool of single colonies obtained after selection). The clones have been obtained from host cells individually transfected with, and selected for stable expression of an individual member of a library comprising variable region-encoding nucleic acid segments, such as antibody V_H and V_L-encoding segments or TcR α and β-, or γ and δ-encoding segments. Selection for stable expression is performed by procedures known in the art, e.g. using selection marker genes. In a preferred embodiment of the present invention the individual cell lines are obtained from cloned or subcloned cells, e.g. by subjecting a cell

line originating from i) or ii) (see previous description) to limiting dilution or single cell FACS analysis and selection, or by selecting high expression clones e.g. using a robot like the ClonePix FL (see below). The individual cell lines used to generate the pWCB as described above may be pre-stored in a frozen library stock of individual cell lines, from which an ampoule of each individual cell line is thawn and expanded prior to the generation of a pWCB. Preferably, the individual cell lines express full-length antibodies with properties that differ from the properties of the antibodies produced by the other members of the pWBC, e.g. different antigen specificity, different affinity, different variable or CDR regions and/or different constant regions.

Each cell line used to generate the pWCB, produces a different member of a polyclonal protein. Preferably, each distinct member of the polyclonal protein binds a particular antigen. Additionally, it is preferred that each distinct member is produced from a single specific site in the genome of each host cell. A pWCB is generated by mixing a predefined number of cells from each individual cell line. Preferably, the cells are mixed in equal numbers (a 1:1 ratio), although other ratios also may be desired (see later). The mixture of cells is frozen down in aliquots, in that they are distributed into a number of vials with a defined number of cells in each vial. These vials are frozen and stored as the pWCB for later manufacturing purposes. Preferably, the number of vials constituting the pWCB exceeds 10, 25, 50, 75, 100, 200, 500 or 1000 vials. The individual vials in a pWCB may be thawn at different points in time generating different batches of the polyclonal manufacturing cell line which are capable of producing a polyclonal protein with essentially the same composition from batch to batch (See Example 5).

In an alternative approach of the present invention, the polyclonal manufacturing cell line may be expanded from a sub-pWCB, which is derived from a pWCB. The sub-pWCB is generated by thawing a single vial from a pWCB and expanding the cells for a number of generations sufficient to produce a total number of cells which can be frozen down in a new series of aliquots (the sub-pWCB), with approximately the same number of cells in each sub-pWCB aliquot as in the pWCB vial originally used to generate the sub-pWCB. The advantage of this approach is that the pWCB now serves as a master cell bank as known from other recombinant protein production protocols. Thus, in this approach the pWCB may also be termed a polyclonal master cell bank (pMCB). When the sub-pWCB has been exhausted, it is possible to generate a new sub-pWCB from an aliquot of the pWCB/pMCB. This approach will therefore require a significantly lower amount of work than would be required to expand the individual cell lines from the frozen library stock and mixing a new pWCB. Further, in the event that the sub-pWCB is exhausted, the chance of producing further batches of the polyclonal manufacturing cell line, which are capable of producing a polyclonal protein with essentially the same composition from batch to batch is increased. The principle of

generating a pWCB/pMCB and a sub-pWCB from individually transfected host cells is illustrated in Fig. 1B.

The advantage of producing a pWCB or pMCB by mixing individual cell lines which have been obtained by individual transfection, compared to the direct generation of a pWCB of pMCB by bulk transfection or semi-bulk transfection, is that it is possible to perform additional analysis and selections of the individually transfected cell lines prior to generation of the pWBC or pMCB. This may ensure a more stable polyclonal manufacturing cell line which fulfills the diversity requirements already described. In the following pWCB is to be understood as pWCB or pMCB.

In an additional embodiment of the present invention, individual cell lines which have been selected for stable expression of an individual member of a library of variable region-encoding nucleic acid segments as described above, are further characterized with respect to their proliferation rates and/or productivity prior to generation of a pWCB. In a preferred embodiment cell lines with similar proliferation rates or productivity are selected for the generation of a pWCB. Even more preferred, cell lines with similar productivity as well as similar proliferation rates are selected for the generation of the pWCB. Preferably, the cell lines are adapted to serum free suspension culture prior to the characterization of proliferation rates and/or productivity. Alternatively, the parental cells used for transfection are adapted to serum free suspension culture prior to transfection.

Proliferation rates can be assessed by methods known in the art, for example as described in example 2 of the current invention. Proliferation rates for mammalian cell lines should be between 18 and 100 hours, preferably between 22 and 40 hours and most preferred between 24 and 32 hours. The productivity should exceed 0.5 pg protein per cell per day (pg/(cell*day)), preferably it should exceed 1, 1.5, 3, 5 or 8 pg/(cell*day). Further, the cell line should show a homogenous cell population with respect to expression when assessed by an intra-cellular staining method. If desired a more homogeneous cell population for each individual cell line can be obtained by cloning e.g. by the FACS sorting methods described below.

In further embodiments of the present invention, the individual cell lines are FACS sorted to identify cells with a homogeneous expression level, after the transfection and selection procedures. The possibility of sorting for individual high-expressing clones or a sub-pool of cells with high expression levels by gating on a particular area of the population in connection with the FACS analysis is therefore an additional embodiment of the present invention. The generation of cloned cells by FACS analysis and selection is particularly useful when the individual cell lines are generated from a pool of clones.

Fluorescence labeled antibodies can be used to sort for cells expressing high levels of the desired protein e.g. antibody or TcR, thereby creating a homogeneous cell population with respect to productivity. This technique is based on the observation that secreted proteins can be detected on the surface of the cell secreting them, and the amount of surface protein apparently corresponds to the expression levels of the individual cell. The high producing cells can therefore be single cell sorted upon staining with a labeled antibody, followed by analysis by FACS. The technique has been described by Brezinsky (Brezinsky *et al.* J. 2003. Immunol Methods 277, 141-155).

An alternative sorting technique is based on the coupling of a ligand, with specificity to the protein expressed from the cells, to the surface of the cells. For example an anti-Fc antibody or an anti-idiotype antibody can be coupled to the surface of the protein secreting cell population via biotin. The antibodies secreted by an individual cell are then captured by the anti-Fc antibodies on the surface of that cell. Following this, the high producing cells can be sorted by FACS upon staining with a labeled antibody. This technique has been described in EP 667896.

To obtain cell lines with a homogeneous high expression levels, single cells having a high expression level are analyzed based on the FACS profile obtained by one of the described techniques. The individual cell clones are then expanded and potentially analyzed with respect to proliferation rates and productivity as described above. Alternatively, a sub-pool of cells having the highest expression level as identified by the FACS profile is collected by sorting. The sub-pool of cells from the individual cell line can likewise be analyzed with respect to proliferation rates and productivity if desired.

In an alternative embodiment of this invention, a robot such as the ClonePixFL robot (Genetix, UK) is used to select clones exhibiting high expression levels and/or similar growth properties. This is done as follows: The colonies obtained after transfection and selection are grown in a semi-solid medium which allows for detection of high-producing colonies by capturing the secreted protein product in the immediate proximity of the colony. The production level from each colony is determined by means of immunofluorescence labeling of the protein expressed by the cells followed by image software selection of the best clones based on predetermined selection criteria such as expression level and growth properties. Furthermore, the size (reflecting the cell proliferation rate) of each colony can be assessed by the robot using light detection imaging. Colonies with the desired production and/or growth properties are then isolated by the robot and transferred to 96-well plates for further propagation.

Preferably, individual cell lines with similar productivity are selected for the generation of the pWCB. In a preferred embodiment individual cell lines constituting the pWCB are generated

from cloned cells, e.g. obtained by single cell sorting, limiting dilution or robot picking, with a high expression level or from a pool of cells with high expression level.

In the present invention, both individual cell lines obtained from a single colony of cells isolated after transfection and selection as well as individual cell lines obtained from a clone obtained e.g. by single cell FACS sorting, are termed cloned cell lines. In a preferred embodiment such cloned cell lines are used to generate the pWCB.

In further embodiments of the present invention, the individual cell lines are mixed at different ratios upon generation of a pWCB. The individual cell lines can be mixed according to predetermined criteria based on the properties of the individual cell lines and/or individual protein member expressed by said cell line, e.g. specific productivity or binding affinity. For example, individual cell lines expressing certain antibodies binding particularly critical antigens or epitopes can be supplied in excess of the remaining member cell lines of the pWCB, e.g. in 2-fold, 3-fold, 5-fold or 10-fold higher amounts. One member cell line may for example be added in a 2:1 ratio over all the other members, e.g. 4×10^6 cells of member 1 and 2×10^6 cells of each of the remaining member cell lines.

In a preferred embodiment of the present invention, a pWCB for production of an Anti-RhD rpAb is generated. Even more preferred such a pWCB is generated such that cell lines which produce antibodies with reactivity against a RhD category VI antigen constitute at least 5%, 8%, 10%, 12%, 15%, 20% or 25% of the total amount of cells included in the pWCB.

This approach of differentiated ratios of the individual cell lines in the pWCB may also be adopted to circumvent differences in proliferation rates and productivity among the individual cell lines, in particular if these have not been selected for similarity in these traits. Hence, if one or more of the individual cell lines have a slower proliferation rate, i.e. longer doubling times, compared to other members of the polyclonal working cell bank which are characterized by a faster proliferation rate, but this slower proliferation rate is not associated with a particular high productivity, this particular member(s) may be added to the pWCB in an increased amount to compensate for its slow growth. For example may a cell line with a proliferation rate of 50 hours be added in a 2:1 ration if the remaining cell lines constituting the pWCB have proliferation rates between 22 and 30 hours. Likewise, the ratio of cell lines with short doubling times may be reduced to ensure that these will not take over during manufacturing. Further, the ratios of the individual cell lines in a pWCB may be adjusted upon analysis of the polyclonal protein products produced from the polyclonal manufacturing cell lines generated from the pWCB. Such adjustments may for example be made based on IEX profiles or equivalent characterization tools. If such an analysis shows that one or more particular protein members are produced in an increased amount compared to the remaining members, a new pWCB may be generated, wherein the ratio of the cell lines producing these particular protein members are reduced. And visa versa, if a particular member is produced

in a low amount, a pWCB with an increased ratio of the cell line producing this member may be generated.

Purification of an anti-RhD rpAb from culture supernatant

Isolation of anti-RhD rpAb from culture supernatants is possible using various chromatographic techniques that utilize differences in the physico-chemical properties of proteins, *e.g.* differences in molecular weight, net charge, hydrophobicity, or affinity towards a specific ligand or protein. Proteins may thus be separated according to molecular weight using gel filtration chromatography or according to net charge using ion-exchange (cation/anion) chromatography or alternatively using chromatofocusing.

Affinity chromatography combined with subsequent purification steps such as ion-exchange chromatography, hydrophobic interactions and gel filtration has frequently been used for the purification of IgG (polyclonal as well as monoclonal) from different sources e.g., ascites fluid, cell culture supernatants and serum. Affinity purification, where the separation is based on a reversible interaction between the anti-RhD antibodies and a specific ligand coupled to a chromatographic matrix, is an easy and rapid method, which offers high selectivity, usually high capacity and concentration into a smaller volume. Specific ligands in the form of peptides capable of binding to anti-RhD antibodies may be obtained according to the method described in EP 1 106 625 using peptide phage display. Protein A and protein G, two bacterial cell surface proteins, have high affinity for the F_c region, and have, in an immobilized form, been used for many routine applications, including purification of polyclonal IgG and its subclasses from various species and absorption and purification of immune complexes.

Following affinity chromatography, downstream chromatography steps, e.g. ion-exchange and/or hydrophobic interaction chromatography, can be performed to remove host cell proteins, leaked Protein A, and DNA. With the protein A affinity and cation exchange chromatography it has been observed that pH-values above 5 may cause precipitation of the anti-RhD rpAb. Thus buffers should be adjusted carefully with appropriate buffering agents, e.g. Tris or acetate.

Gel filtration, as a final purification step, can be used to remove contaminant molecules such as dimers and other aggregates, and transfer the sample into storage buffer. Depending on the source and expression conditions it may be necessary to include an additional purification step to achieve the required level of antibody purity. Hydrophobic interaction chromatography or ion-exchange chromatography are thus frequently used, in combination with Protein A and gelfiltration chromatography, to purify antibodies for therapeutic use.

In order to purify other classes of antibodies, alternative affinity chromatography media have to be used since proteins A and G do not bind IgA and IgM. An immuno-affinity purification

can be used (anti-IgA or anti-IgM monoclonal antibodies coupled to solid phase) or, alternatively, multistep purification strategies including ion-exchange and hydrophobic interaction can be employed.

Structural Characterization of anti-RhD rpAb

Structural characterization of polyclonal antibodies requires high resolution due to the complexity of the mixture (clonal diversity, heterogeneity and glycosylation). Traditional approaches such as gel filtration, ion-exchange chromatography or electrophoresis may not have sufficient resolution to differentiate among the individual antibodies in the anti-RhD rpAb. Two-dimensional polyacrylamide gel electrophoresis (2D-PAGE) has been used for profiling of complex protein mixtures followed by mass spectrometry (MS) or liquid chromatography (LC)-MS (e.g., proteomics). 2D-PAGE, which combines separation on the basis of a protein's charge and mass, has proven useful for differentiating among polyclonal, oligoclonal and monoclonal immunoglobulin in serum samples. However, this method has some limitations. Chromatographic techniques, in particular capillary and LC coupled to electrospray ionization MS are increasingly being applied for the analysis of complex peptide mixtures. LC-MS has been used for the characterization of monoclonal antibodies and recently also for profiling of polyclonal antibody light chains. The analysis of very complex samples requires more resolving power of the chromatographic system, which can be obtained by separation in two dimensions (or more). Such an approach is based on ion-exchange in the first dimension and reversed-phase chromatography (or hydrophobic interaction) in the second dimension optionally coupled to MS.

Functional Characterization of anti-RhD rpAb

An anti-RhD rpAb antibody can for example be characterized functionally through comparability studies with anti-D immunoglobulin products or anti-RhD mAbs. Such studies can be performed in vitro as well as in vivo.

In vitro functional characterization methods of anti-RhD rpAb could for example be phagocytosis assays (^{51}Cr-based or FACS based), antibody dependent cellular cytotoxicity (ADCC) and rosetting assay. Briefly described the assays are performed as follows:

ADCC assay (^{51}Cr based):
Human PBMC are used as effector cells and RhD negative and positive RBC (0 in the ABO system) are used as targets. First, the RBC (RhD(+) and RhD(-)) are ^{51}Cr labelled, washed and then sensitized with anti-RhD antibodies (e.g. anti-RhD rpAb, anti-D or anti-RhD mAb) in various dilutions. The effector cells (PMBC) are added to the sensitized RBC (ratio of 20:1) and incubation is performed overnight. Cells are spun down and the supernatants from the wells are transferred to a Lumaplate (PerkinElmer). Controls for spontaneous release are

included (RBC with ^{51}Cr only) and for total release (addition of Triton-X-100 to ^{51}Cr-labeled RBC). The Lumaplate is dried and counted in a Topcounter (PerkinElmer).

Phagocytosis assay (^{51}Cr based):
Phagocytosis can be measured in combination with the ADCC assay. After harvesting the supernatant in the ADCC assay, the remaining supernatant is removed and the red blood cells are lysed by addition of a hypotonic buffer. The cells are washed and the supernatant is removed. PBS+1% Triton-X-100 is added to all wells and fixed amounts are transferred to a Lumaplate, dried and counted as before.

Phagocytosis assay (FACS based):
This assay is based on adherence of the phagocytic cells. The human leukemic monoblast cell line U937 can be used for this assay. U937 cells are differentiated using 10nM PMA. Two days later 60% of the medium is removed and replaced by medium without PMA. The cell membrane of red blood cells (RhD(+) and RhD(-)) are stained with PKH26 (PE) according to the manufactures protocol (Sigma). The RBC's are sensitized with anti-RhD antibodies in various dilutions and excess antibodies are removed by washing. On day three, the non-adherent cells U937 cell are removed by washing and sensitized RBC (RhD(+) and RhD(-)) are added to the wells. The plates are incubated overnight in the incubator. Non-phagocytozed RBC are washed away by several steps. Attached but not phagocytozed RBC are lysed by addition of hypotonic buffer followed by additional washing. The U937 cells detached from the wells by incubation with trypsin. Cells are analyzed on the FACS.

Rosetting assay
A rosetting assay is merely an Fc receptor binding assay. Sensitized red blood cells are incubated with differentiated U937 cells prepared as described above. RBC (RhD (-) and RhD(+)) are sensitized with anti-RhD antibodies in various dilutions and excess antibodies are removed by washing before they are mixed with U937 cells. Incubation is performed for one hour and non-bound RBC are washed away. The percentage of cells with two or more RBC attached to the surface is counted.

An in vivo functional characterization of anti-RhD antibodies is described by Miescher (Miescher, S., et al. 2004, Blood 103, 4028-4035), an involves injection of RhD(+) cells into RhD(-) individuals followed by administration of anti-RhD antibody. RBC clearance and anti-RhD antibody sensation of the donors was analyzed.

Therapeutic compositions

In an embodiment of the invention, a pharmaceutical composition comprising anti-RhD rpAb or anti-RhD recombinant polyclonal Fab or another anti-RhD recombinant polyclonal fragment as active ingredient is intended for the prophylaxis of hemolytic disease of the newborn,

treatment of idiopathic thrombocytopenic purpura (ITP) or prevention of sensitization to the Rhesus D antigen after mistransfusions of RhD(+) blood to RhD(-) individuals.

The pharmaceutical composition further comprises a pharmaceutically acceptable excipient.

Anti-RhD rpAb or polyclonal fragments thereof may be administered within a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer to female mothers or patients. In a preferred embodiment the administration is prophylactic. Any appropriate route of administration may be employed, for example, administration may be parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intraperitoneal, intranasal, aerosol, suppository, or oral administration. For example, therapeutic formulations may be in the form of, liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets or capsules chewing gum or pasta, and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example, by means of conventional dissolving, lyophilizing, mixing, granulating or confectioning processes. The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice (see for example, in Remington: The Science and Practice of Pharmacy (20th ed.), ed. A.R. Gennaro, 2000, Lippincott Williams & Wilkins, Philadelphia, PA and Encyclopedia of Pharmaceutical Technology, eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York, NY).

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilized compositions that comprise the active ingredient alone or together with a carrier, for example mannitol, for such solutions or suspensions to be produced prior to use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting and/or emulsifying agents, solubilizers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

The injection compositions are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into ampoules or vials and sealing the containers.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the

mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, pills, or capsules, which may be coated with shellac, sugar or both. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, tablets, pills, or capsulesThe formulations can be administered to human individuals in therapeutically or prophylactic effective amounts (e.g., amounts which prevent, eliminate, or reduce a pathological condition) to provide therapy for a disease or condition. The preferred dosage of therapeutic agent to be administered is likely to depend on such variables as the type and extent of the disorder, the overall health status of the particular patient, the formulation of the compound excipients, and its route of administration.

Therapeutic uses of the compositions according to the invention

The pharmaceutical compositions according to the present invention may be used for the treatment, amelioration or prophylaxis of a disease in a mammal. Conditions that can be treated or prevented with the present pharmaceutical compositions include prevention of hemolytic disease of the newborn, treatment of idiopathic thrombocytopenic purpura (ITP) or prevention of sensitization to the Rhesus D antigen after mistransfusions of RhD(+) blood to RhD(-) individuals.

One aspect of the present invention is a method for disease treatment, amelioration or prophylaxis in an animal, wherein an effective amount of anti-RhD rpAb or fragment is administered.

A further embodiment of the present invention is the use of an anti-RhD recombinant polyclonal antibody or polyclonal antibody fragment for the preparation of a composition for the prophylaxis of hemolytic disease of the newborn or treatment of idiopathic thrombocytopenic purpura (ITP).

Diagnostic use and environmental detection use

Another embodiment of the invention is directed to diagnostic kits. Kits according to the present invention comprise an anti-RhD rpAb prepared according to the invention which protein may be labeled with a detectable label or non-labeled for non-label detection. The kit may be used to identify RhD(+) individuals, or individuals with a particular Rhesus D category. Identification of the later can be achieved by having a anti-RhD rpAb composition which only react with that particular Rhesus D category.

EXAMPLES

The following examples describe how anti-RhD rpAb is expressed and produced in a high-producer cell line, where V_H and V_L comprising nucleic acid segments or vector(s) have been inserted by site-specific integration into a pre-characterized chromosomal "hot-spot" site.

In the examples, CHO cells were utilized as host cell. The advantages thereof include the availability of suitable growth medium, their ability to grow efficiently to a high density in culture, and their ability to express mammalian proteins such as antibodies in a biologically active form.

In general, transformation of *E. coli* and transfection of mammalian cells according to the subject invention will be performed according to conventional methods.

The following examples illustrate the invention, but should not be viewed as limiting the scope of the invention.

EXAMPLE 1

Production of an anti-Rhesus D recombinant polyclonal antibody

Donors

Donors were enrolled at Aalborg Sygehus Nord. A total of eight RhD(-) women were immunized with RhD(+) erythrocytes derived from RhD(+) individuals. The donors had a varying history of the immunizations with respect to the number of boosts and the origin of RhD(+) erythrocytes for the immunization. The immunization history of the different donors is given in the table 1.

Table 1

Donor #	# of boost	# of boosts from different origin
1	3	2
2	6	2
3	2	1
4	4	4
5	2	2
6	3	2
7	2	2
8	2	2

Mononuclear cells were harvested by leukopheresis 5-7 days after the last boost. The cells were pelleted and immediately transferred to the cell lysis solution from a commercially available RNA preparation kit (NucleoSpin RNA L, Machery-Nagel, cat. no. 740 962.20). After lysis of the cells, the suspension was frozen before further processing.

Generation of Anti-Rhesus D Fab display library

The material obtained from each donor was kept separate throughout the procedure of library generation and panning. The cell lysates were thawed and RNA was prepared according to kit instructions (NucleoSpin RNA L). The integrity of the RNA was analyzed by agarose gel electrophoresis, thus verifying that the 18S/28S ribosomal RNAs were not degraded.

RNA was subjected to cDNA synthesis in an oligo(dT) primed reaction using approximately 10 µg total RNA in a reaction using ThermoScript (Invitrogen), according to the manufacturer's instructions. The cDNA was used as template in PCR reactions using the following primers:

V_H forward primers (XhoI site in bold):

J region	SEQ ID	Primer sequence
JH1/2	2	GGAGGCG**CTC GAG**ACGGTGA CCAGGGTGCC
JH3	3	GGAGGCG**CTC GAG**ACGGTGA CCATTGTCCC
JH4/5	4	GGAGGCG**CTC GAG**ACGGTGA CCAGGGTTCC
JH6	5	GGAGGCG**CTC GAG**ACGGTGA CCGTGGTCCC

V_H reverse primers (AscI site in bold):

V gene family	SEQ ID	Primer sequence
1B/7A	6	CCAGCCGG**GG CGCGCC**CAGR TGCAGCTGGT GCARTCTGG
1C	7	CCAGCCGG**GG CGCGCC**SAGG TCCAGCTGGT RCAGTCTGG
2B	8	CCAGCCGG**GG CGCGCC**CAGR TCACCTTGAA GGAGTCTGG
3B	9	CCAGCCGG**GG CGCGCC**SAGG TGCAGCTGGT GGAGTCTGG
3C	10	CCAGCCGG**GG CGCGCC**GAGG TGCAGCTGGT GGAGWCYGG
4B	11	CCAGCCGG**GG CGCGCC**CAGG TGCAGCTACA GCAGTGGGG
4C	12	CCAGCCGG**GG CGCGCC**CAGS TGCAGCTGCA GGAGTCSGG
5B	13	CCAGCCGG**GG CGCGCC**GARG TGCAGCTGGT GCAGTCTGG
6A	14	CCAGCCGG**GG CGCGCC**CAGG TACAGCTGCA GCAGTCAGG

C_κ forward primer (NotI site in bold):

SEQ ID	Primer sequence
15	ACCGCCTCCA CCG**GCGGCCG C**TTATTAACA CTCTCCCCTG TTGAAGCTCT T

V_κ reverse primers (NheI site in bold):

V gene family	SEQ ID	Primer sequence
1B	16	CAACCAGC**GC TAGC**CGACAT CCAGWTGACC CAGTCTCC
2	17	CAACCAGC**GC TAGC**CGATGT TGTGATGACT CAGTCTCC
3B	18	CAACCAGC**GC TAGC**CGAAAT TGTGWTGACR CAGTCTCC
4B	19	CAACCAGC**GC TAGC**CGATAT TGTGATGACC CACACTCC
5	20	CAACCAGC**GC TAGC**CGAAAC GACACTCACG CAGTCTCC
6	21	CAACCAGC**GC TAGC**CGAAAT TGTGCTGACT CAGTCTCC

C_λ forward primer (NotI sit in bold):

λ family	SEQ ID	Primer sequence
2	22	ACCGCCTCCACCG**GCGGCCGC**TTATTATGAACATTCTGTAGGGCCACTG
7	23	ACCGCCTCCACCG**GCGGCCGC**TTATTAAGAGCATTCTGCAGGGGCCACTG

V_λ reverse primers (NheI in bold):

V gene family	SEQ ID	Primer sequence
1A	24	CAACCAGC**GC TAGC**CCAGTC TGTGCTGACT CAGCCACC
1B	25	CAACCAGC**GC TAGC**CCAGTC TGTGYTGACG CAGCCGCC
1C	26	CAACCAGC**GC TAGC**CCAGTC TGTCGTGACG CAGCCGCC
2	27	CAACCAGC**GC TAGC**CCARTC TGCCCTGACT CAGCCT
3A	28	CAACCAGC**GC TAGC**CCTTTC CTATGWGCTG ACTCAGCCACC
3B	29	CAACCAGC**GC TAGC**CCTTTC TTCTGAGCTG ACTCAGGACCC
4	30	CAACCAGC**GC TAGC**CCACGT TATACTGACT CAACCGCC
5	31	CAACCAGC**GC TAGC**CCAGGC TGTGCTGACT CAGCCGTC
6	32	CAACCAGC**GC TAGC**CCTTAA TTTTATGCTG ACTCAGCCCCA
7/8	33	CAACCAGC**GC TAGC**CCAGRC TGTGGTGACY CAGGAGCC
9	34	CAACCAGC**GC TAGC**CCWGCC TGTGCTGACT CAGCCMCC

PCR was performed with individual primer pairs amounting to 36 V_H reactions, 6 Kappa reactions and 22 Lambda reactions. All V_H, Kappa, and Lambda PCR products were pooled separately and following purification using NucleoSpin columns (Machery-Nagel, cat. no. 740

590.250), the products were digested prior to cloning (V_H: AscI/XhoI, Kappa and Lambda: NheI/NotI) followed by a gel purification step of the bands of interest (PerfectPrep Gel Cleanup kit, Eppendorf, cat. no. 0032 007.759). The light chains (Kappa and Lambda separately) were inserted into a NheI/NotI treated Em351 phage display vector (Fig. 2), by ligation and amplified in *E.coli* XL1 Blue (Stratagene). Plasmid DNA constituting the light chain library was isolated from the *E.coli* cells selected over night on Carbenicillin agar plates (two libraries for each donor, Kappa and Lambda, respectively). This library DNA was subjected to digest with AscI/XhoI, and after gel purification, the V_H PCR products (subjected to digest with the same enzymes and gel purified) were ligated into the two light chain libraries from each donor and amplified in *E.coli* TG1 cells (Stratagene) using Carbenicillin selection on agar plates. After overnight growth, bacteria were scraped off the plates, and glycerol stocks were prepared for proper library storage. A plasmid DNA preparation containing the combinatorial variable heavy chain - light chain (V_H:LC) library was also performed to secure the library for the future. The combinatorial libraries contained in the TG1 cells (two from each donor) were now ready for phage display and panning. The sizes of the combinatorial libraries (16 in total) were 10^6 or larger.

Enrichment for phages displaying Rhesus D antigen binding Fab fragments

Phages displaying Fabs on their surface were generated as follows: 50 mL 2 x YT/1% glucose/100 µg/mL Carbenicillin was inoculated with TG1 cells containing the combinatorial V_H:V_L library to obtain an OD_{600} of approximately 0.08. The culture was shaking for 1½ h, and helper phage was added (VSCM13). The culture was incubated at 37°C for ½ h without shaking and for ½ h with shaking. The bacteria were pelleted (3200 x g, 10 minutes, 4°C), and re-suspended in 50 mL 2 x YT/100 µg/mL Carbenicillin/70µg/mL Kanamycin, and the culture was shaken overnight at 30°C. The phages were precipitated from the culture supernatant by adding 1/5 volume of 20% PEG/1.5 M NaCl, incubating on ice for 30 minutes, and centrifugation at 8000 x g for 30 minutes at 4°C. Precipitated phages were resuspended in PBS and used directly for panning.

Panning for Rhesus D antigen binding Fab fragments was performed in a two-step procedure. 10^8 RhD(-) red blood cells (RBC) were washed three times in PBS (centrifugation at 2000 x g, 45 sec), and re-suspended in 150 µl panning buffer (2 % skim milk in 0.85 x PBS). Fifty µl freshly prepared phages were added to the RhD(-) cells (re-suspended in panning buffer) in order to perform a negative selection step, and incubated for 1 h on an end-over-end rotator at 4°C. Following the one hour incubation, the cells were pelleted by centrifugation (2000 x g, 45 sec), and the phage-containing supernatant was incubated with 2 x 10^7 RhD(+) RBC (washed three times in PBS). The phage:RhD(+) RBC mix was incubated for one hour on an end-over-end rotator at 4°C. Unbound phages were removed by washing five times with 1 mL panning buffer, and five times with PBS. Bound phages were eluted by addition of 200 µl

H_2O (which lyses the cells). One hundred µl of the eluate was added to exponentially growing TG1 cells, the remainder was stored at -80°C. TG1 cells infected with eluated phages were plated on Carb/glu agar dishes and incubated overnight at 37°C. The following day, the colonies were scraped off the plates, and 10 mL culture medium was inoculated for preparation of phages for the second round of panning. The second round of panning was performed as described for the first round.

Enrichment for phages displaying Rhesus D category VI antigen binding Fab fragments

In a separate set of pannings, selections were performed in order to retrieve clones with reactivity towards the RhD category VI antigen. The negative selection was performed on RhD(-) blood as described, and the positive selection was performed on RhD^{VI} positive erythrocytes. The procedure was otherwise as described above.

Screening for anti-RhD binding Fabs

After each round of panning single colonies were picked for analysis of their binding properties to red blood cells in agglutination assays. Briefly, single colonies were inoculated into 2 x YT/100 µg/mL carbenicillin/ 1% glucose and shaken overnight at 37°C. The next day, DeepWell plates were inoculated using 900 µl 2 x YT/100 µg/mL carbenicillin/0.1% glucose and 10 µl overnight culture. The plates were shaken for two hours at 37°C, before Fab induction was performed with addition of 300 µl 2 x YT/100 µg/mL carbenicillin/0,25 mM IPTG per well. The plate was shaken overnight at 30°C. The following day, the bacteria were pelleted by centrifugation (3200 x g, 4°C, 10 minutes), and re-suspended in 100 µl of 0,8 M NaCl, 0,2 x PBS, 8 mM EDTA, and incubated for 15 minutes on ice in order to perform a periplasmic extraction of the Fab fragments. The plate was transferred to -20°C and finally the suspension was thawed and centrifugation was performed for 10 minutes at 4°C and 3200 x g. The periplasmic extract was used in ELISA assays for analysis of Fab content and in agglutination assays to evaluate the binding potential of the individual Fab fragments.

The agglutination assay was performed as follows: RhD(-) and RhD(+) RBC were mixed in a 1:1 ratio, and washed 3 times in PBS. After the final wash, the cell mix was re-suspended in 1% BSA in PBS at a density of 1% cells, 50 µl was added to each well of a 96-plate. Periplasmic extracts were added to the wells. As a positive control Rhesogamma P immunoglobulin (Aventis) was used according to the manufacturer's instructions. The plates were incubated for one hour at room temperature with gentle shaking. The cells were washed three times with PBS, before the secondary antibody was added (goat anti-human Fab/FITC conjugate, Sigma F5512) in a 1:100 dilution. The plates were left for agglutination for one hour at room temperature without shaking. Fab fragments positive in the agglutination assay was determined by visual inspection, and recorded by taking a picture. Quantization of the

binding activity of the Fab fragments was performed by FACS analysis of the agglutination samples.

When performing screening for clones with reactivity towards RhD^{VI}+ erythrocytes, such cells were used in conjunction with RhD(-) cells in a procedure otherwise identical to that described above.

Selection of diverse anti-RhD Fab-encoding sequences

A total of 1700 RhD antigen binding clones were identified. All the positive clones were submitted for DNA sequencing. From these 56 clones were selected based on their unique set of heavy chain CDR sequences. For multiple clones which used the same heavy chain with different light chains, the clone which showed the highest binding activity in the FACS assay was selected. Thereby a sub-library comprised of pairs of variable heavy chain (V_H) and light chain (LC)-encoding sequences, representing a broad diversity with high RhD antigen specificity, was selected from all the positive clones.

The binding activity of these 56 clones was re-confirmed in agglutination assays, to ensure no false positive clones were selected.

The selected clones were further analyzed with respect to mutations due to for instance inter-family cross-priming, since such mutations may lead to overall structural changes of the expressed antibody possibly creating new epitopes and thereby result in an increased immunogenicity of the final product. Clones with such mutations were repaired as described in the following section relating to V_H:LC transfer from the phagemid vector to the mammalian expression vector.

Alignments of the corrected nucleic acid sequences for the V_H and light chains (LC) are shown in Fig 3 to 6, respectively. Further alignments of the V_H and V_L polypeptide chains are shown in figure 5 and 6, respectively. The polypeptide alignments were performed and numbered according to structural criteria defined by Chothia (Chothia *et al.* 1992 J. Mol. Biol. 227, 776-798; Tomlinson *et al.* 1995 EMBO J. 14, 4628-4638 and Williams *et al.* 1996 J. Mol. Biol., 264, 220-232). The figures further indicate the position of the three CDR regions within the variable regions. The CDR region positions within the amino acid sequences are summarized in table 2. The numbering of the CDR3 regions in the polypeptide alignments (Fig. 5 and 6) does not follow Chothia (transition marked with an asterisk in the figures). In order to enable identification of the CDR3 region with respect to amino acid position, a continued numbering has been assigned after the asterisk. The CDR3 region sequence for each individual clone can be derived from the figures based on this numbering.

Table 2

	V_H a.a. position	V_L Kappa a.a. position	V_L Lambda a.a. position
Figure	**5**	**6A**	**6B**
CDR1	31-35	24-34	25-35
CDR2	50-65	50-56	53-57
CDR3	95-125	89-110	90-113

The pairs of variable heavy chain and complete light chain which have been screened as Fabs and selected for their ability to bind RhD antigen can be identified by their identical clone numbers. All the 56 V_H:LC pairs are listed by clone number, the nucleic acid (nuc.) SEQ IDs and the amino acid (a.a.) SEQ IDs in table 3.

Table 3

Clone Name	V_H nuc. SEQ ID	LC nuc. SEQ ID	V_H a.a. SEQ ID	LC a.a SEQ ID	Clone Name	V_H nuc. SEQ ID	LC nuc. SEQ ID	V_H a.a. SEQ ID	LC a.a. SEQ ID
RhD157.119D11	35	91	147	203	RhD240.125A09	63	119	175	231
RhD158.119B06	36	92	148	204	RhD241.119B05	64	120	176	232
RhD159.119B09	37	93	149	205	RhD242.181A03	65	121	177	233
RhD160.119C07	38	94	150	206	RhD243.109A05	66	122	178	234
RhD161.119E09	39	95	151	207	RhD244.158B10	67	123	179	235
RhD162.119G12	40	96	152	208	RhD245.164E06	68	124	180	236
RhD163.119A02	41	97	153	209	RhD246.179B10	69	125	181	237
RhD189.181E07	42	98	154	210	RhD292.109A02	70	126	182	238
RhD190.119F05	43	99	155	211	RhD293.109A09	71	127	183	239
RhD191.119E08	44	100	156	212	RhD294.119E10	72	128	184	240
RhD192.119G06	45	101	157	213	RhD295.119B11	73	129	185	241
RhD193.126G05	46	102	158	214	RhD296.126A03	74	130	186	242
RhD194.126G10	47	103	159	215	RhD297.126E06	75	131	187	243
RhD195.127A07	48	104	160	216	RhD298.126E10	76	132	188	244
RhD196.126H11	49	105	161	217	RhD299.127A12	77	133	189	245
RhD197.127A08	50	106	162	218	RhD300.134H09	78	134	190	246
RhD198.127F10	51	107	163	219	RhD301.160A04	79	135	191	247
RhD199.164E03	52	108	164	220	RhD302.160B10	80	136	192	248
RhD200.164G10	53	109	165	221	RhD303.160B11	81	137	193	249
RhD201.164H12	54	110	166	222	RhD304.164B06	82	138	194	250
RhD202.158E07	55	111	167	223	RhD305.181E06	83	139	195	251
RhD203.179F07	56	112	168	224	RhD306.223E11	84	140	196	252
RhD204.128A03	57	113	169	225	RhD307.230E11	85	141	197	253
RhD205.160B12	58	114	170	226	RhD317.144A02	86	142	198	254
RhD206.160C06	59	115	171	227	RhD319.187A11	87	143	199	255
RhD207.127A11	60	116	172	228	RhD321.187G08	88	144	200	256
RhD208.179B11	61	117	173	229	RhD323.229B07	89	145	201	257
RhD239.126F09	62	118	174	230	RhD324.231F07	90	146	202	258

Transfer of the selected V_H and light chain-encoding sequences to a mammalian expression vector.

Due to the mutations resulting from, for instance, inter-family cross-priming it was necessary to repair of a large number of the selected sequences. This was done in connection with exchange of expression system from phage display to mammalian expression. For this reason the transfer was performed separately for each individual clone.

The transfer and repair was performed as follows: First the V_H-encoding sequence situated in the Em351 vector was re-amplified by PCR using the high fidelity polymerase, Phusion (Finnzymes) and a proper set of correcting primers. The V_H PCR fragment was digested with AscI and XhoI and subjected to gel purification. The Neo exp. vector (Fig. 7) was digested with the corresponding enzymes and gel purified thereby removing the nucleic acid sequence situated between the leader sequence and the heavy chain constant regions. The corrected V_H fragment and the Neo exp. vector were ligated and amplified in *E.coli* Top10 cells. Plasmid DNA of the V_H containing Neo exp. vector was isolated from the *E.coli* cells selected over night on Carbenicillin.

Following transfer of the V_H-encoding sequence the corresponding LC sequence was re-amplified by PCR using the high fidelity polymerase, Phusion (Finnzymes) and a proper set of correcting primers. The LC PCR fragment was digested with NheI and NotI and subjected to gel purification. The V_H containing Neo exp. vector was digested with the corresponding enzymes and gel purified thereby removing the nucleic acid sequence situated between the kappa leader sequence and the BGHpolyA signal sequence. The corrected LC fragment and the V_H containing Neo exp. vector were ligated and amplified in E.coli Top10 cells. Glycerol stocks were prepared for each individual clone, and a high quality plasmid preparation suitable for transfection of mammalian cells was prepared from the bacterial cultures as well.

By performing the transfer separately for each clone the V_H:LC pairs originally selected by phage display were regenerated in the mammalian expression vector. In the instances where repair was not necessary the nucleic acid segment was transferred without performing PCR prior to the digestion with the appropriate restriction enzymes.

The mammalian expression vectors generated by the transfer described are suitable for expressing a full-length anti-RhD recombinant polyclonal antibody. Although the vectors are kept separate at this point it is still considered as a library of anti-RhD antibody expression vectors.

Transfection and selection of mammalian cell lines

The Flp-In CHO cell line (Invitrogen) was used as starting cell line for establishment of a recombinant polyclonal manufacturing cell line. However, to obtain a more homogenous cell

line the parental Flp-In CHO cell line was sub-cloned. Briefly, the parental cell line was sub-cloned by limited dilution and several clones were selected and expanded. Based on growth behavior one clone, CHO-Flp-In (019), was selected as production cell line.

All the 56 plasmid preparations were transfected individually into the CHO-Flp-In (019) cell line as follows: the CHO-Flp-In (019) cells were cultured as adherent cells in F12-HAM with 10% fetal calf serum (FCS). 2.5 x 10^6 cells were transfected with plasmid representing one clone using Fugene6 (Roche). Cells were trypsinated 24 hours after transfection and transferred to 3 x T175 flasks. Selection pressure, in this case 450 µg/ml Neomycin, was added 48 hours after transfection. Approximately two weeks later clones appeared. Clones were counted and cells were trypsinated and hereafter cultured as pools of clones expressing one of the 56 specific anti-Rhesus-D antibodies.

Adaptation to serum free suspension culture

The individual adherent anti-Rhesus-D antibody CHO-Flp-In (019) cell cultures were trypsinated, centrifuged and transferred to separate shaker flasks with 8 x 10^5 cells/ml in appropriate serum free medium (Excell302, JRH Biosciences).

Growth and cell morphology were followed over several weeks. When cells showed good and stable growth behavior and had doubling time below 32 hours 50 aliquots of each culture with 10 x 10^6 cells/tube were frozen down (56x50 aliquots).

Characterization of cell lines

All the individual cell lines were characterized with respect to antibody production and proliferation. This was performed with the following assays:

Production:
The production of recombinant antibodies in the individual cultures were followed over time by Kappa or Lambda specific ELISA. ELISA plates were coated overnight with goat-anti-human Kappa (Caltag) or goat-anti-human Lambda (Caltag) antibodies in carbonate buffer, pH 9.6. Plates were washed 6 times with washing buffer (1 x PBS and 0.05% Tween 20) and blocked for 1 hour with washing buffer with 2% milk. Samples were added to wells and plates were incubated for 1 hour. Plates were washed 6x and secondary antibodies (goat-anti-human IgG (H+L) HRPO, Caltag) were added for 1 hour followed by 6x wash. ELISA was developed with TMB substrate and reaction stopped by addition of H_2SO_4. Plates were read at 450 nm.

Further, intracellular FACS staining, using fluorescently tagged antibodies was used to measure the production of recombinant antibodies in the cell culture system. 5 x 10^5 cells were washed in cold FACS PBS (1x PBS ad 2% FCS) and centrifuged. Cells were fixed in

CellFix (BD-Biosciences) for 20 min and hereafter washed in saponin buffer (1x PBS and 0.2% Saponin). The suspension was centrifuged and fluorescently tagged antibody (Goat $F(ab')_2$ Fragment, Anti-human IgG(H+L)-PE, Beckman Coulter) was added for 20 min on ice. Cells were washed twice in saponin buffer and resuspended in FACS buffer and analyzed by FACS. This intracellular staining was used to determine the general expression level as well as to determine the homogeneity of the cell population in relation to expression of recombinant antibodies.

Proliferation:
Aliquots of cell suspension were taken three times a week and cell number, cell size, degree of clumping and percentage of dead cells were determined by CASY® (Cell Counter + Analyzer System from Schärfe System GmbH) analysis. The doubling time for the cell cultures was calculated by cell number derived form CASY® measurements.

Establishment of a manufacturing cell line for anti-Rhesus D recombinant polyclonal antibody production

Ten cell lines each expressing a distinct recombinant anti-Rhesus-D antibody (RhD157.119D11, RhD158.119B06, RhD159.119B09, RhD161.119E09, RhD163.119A02, RhD190.119F05, RhD191.119E08, RhD192.119G06, RhD197.127A08 and RhD204.128A03) were selected to constitute the recombinant polyclonal manufacturing cell line. The Rhd197 and RhD204 were lambda clones whereas all the others were kappa clones.

After the cell cultures expressing the individual anti-Rhesus antibodies were fully adapted to serum free suspension culture in shaker flasks they were mixed in equal cell number, thereby generating a polyclonal CHO-Flp-In (019) cell line. The mixed cell culture was centrifuged and frozen down in aliquots of 10×10^6 cells/tube.

Two tubes (3948 FCW065 and 3949 FCW065) were thawed and cultured individually for 11 weeks in 1000 ml shaker flasks containing 100 ml Excell302 medium with neomycin.

The supernatant was harvested and filtered prior to purification of the anti-RhD rpAb.

Clonal Diversity

The clonal diversity was assayed both on the protein level as well as on the mRNA level. The supernatant sample used to analyze the antibody composition was taken after 9 weeks of cultivation, whereas the cell sample used to analyze the mRNA composition was taken at the harvest after 11 weeks of cultivation.

Antibody composition:

The anti-RhD rpAb expressed from the polyclonal CHO-Flp-In (019) cell line is an IgG1 isotype antibody. Anti-RhD rpAb was purified from both aliquots (3948 and 3949) using a column with immobilized Protein A. The individual antibodies interacted with immobilized Protein A at pH 7.4, whereas contaminating proteins were washed from the column. The bound antibodies were subsequently eluted from the column at low pH value (pH 2.7). The fractions containing antibodies, determined from absorbance measurements at 280 nm, were pooled and dialyzed against 5 mM sodium acetate pH 5.

The anti-RhD rpAb compositions obtained from aliquot 3948 and 3949 (FCW065) after 9 weeks of cultivation were analyzed using cation exchange chromatography. The Protein A purified anti-RhD rpAb was applied onto a PolyCatA column (4.6 x 100 mm) in 25 mM sodium acetate, 150 mM sodium chloride, pH 5.0 at a flow rate of 60 ml h^{-1} operated at room temperature. The antibody components were subsequently eluted using a linear gradient from 150 – 350 mM sodium chloride in 25 mM sodium acetate, pH 5.0 at a flow rate of 60 ml h^{-1}. The antibody components were detected spectrophotometrically at 280 nm. The chromatogram (Fig. 8) was subsequently integrated and the area of the individual peaks A-J was subsequently used to quantitate antibody components (table 4). The total area of the peaks was set to 100 %. The chromatograms from the two aliquots showed an identical peak distribution, as well as similar concentrations of the components in each peak. From these results it can be concluded that aliquots of the same polyclonal cell line grown under identical conditions will produce anti-RhD rpAb with a similar clonal diversity.

The individual members of the anti-RhD rpAb were allocated to one or more particular peaks (summarized in table 4). The allocation is based on chromatograms obtained for antibody products from each individual clone. No individual chromatogram was obtained for antibodies produced from RhD158.119B06, thus this clone was not assigned to any of the peaks. However it is considered likely that peak D constitute RhD158.119B06, the clone may also be represented in some of the other peaks due to heterogeneity. In particular the antibody product from clone RhD197.127A08 has a high degree of heterogeneity. Clone RhD190.119F05 should have been visible at 15.3 min. However, it was not detectable, indicating that this clone has been lost from the recombinant polyclonal manufacturing cell line. The loss of clone RhD190.119F05 corresponds to a 10% reduction of diversity which is considered acceptable with respect to diversity of the final anti-RhD rpAb composition.

Table 4

Peak	Quantity 3948 (% area)	Quantity 3949 (% area)	Clone name	Comment
A	5.1	5.1	RhD157.119D11	Clone is also present in peak B
B	12.0	10.2	RhD157.119D11 RhD159.119B09 RhD192.119G06	This peak represent at least three different clones
C	5.2	5.3	RhD191.119E08	
D	1.2	0.8	(RhD158.119B06)	Not actually allocated to this peak, but it is likely to be. May also be represented in other peaks.
E	10.9	14.4	RhD204.128A03	
F	24.3	23.0	RhD197.127A08	This clone split into several peaks, due to heterogeneity.
G	13.6	12.5	RhD197.127A08	
H	3.3	4.0	RhD197.127A08	
I	14.0	13.7	RhD161.119E09	
J	10.5	10.5	RhD163.119A02	
			RhD190.119F05	The clone has been lost

mRNA composition:

The clonal diversity within the polyclonal CHO-Flp-In (019) cell line after 11 weeks of cultivation was estimated by RT-PCR-RFLP analysis. Briefly, a cell suspension corresponding to 200 cells were subjected to a freeze-thaw procedure and these lysates were used as template in a RT-PCR using One-STEP RT-PCR kit (Qiagen) with primers amplifying the light chain. The primer sequences were:

forward primer 5'-CGTTCTTTTTCGCAACGGGTTTG (SEQ ID 259)

reverse primer 5'-AAGACCGATGGGCCCTTGGTGGA (SEQ ID 260)

The RT-PCR products were digested with *HinfI* and analyzed by agarose gel electrophoresis, visualizing the restriction product with ethidium bromide staining (Fig. 9).

The expected size of the restriction fragments obtained by *HinfI* digestion of the RT-PCR amplified light chains are shown for each individual clone in table 5. Six unique fragment sizes on the gel, which could be assigned to specific Rhesus D antibody producing clones, are indicated in bold. Not all unique fragments could be identified on the gel, these are indicated in italic. This does, however not necessarily mean that these clones are not represented in the culture, the fragments may either not have been separated sufficiently from other fragments to be identifiable, or their concentration is to weak compared to the stronger bands. This may be more pronounced for shorter fragments, since they bind a smaller number of ethidium bromide molecules and therefore are less visible.

Table 5

RhD #	157	158	159	161	163	190	191	192	197	204
HinfI fragment size	**825**	671	505	**696**	505	502	*475*	671	**743**	*521*
	138	138	**320**	138	*166*	*191*	**268**	*149*	138	**167**
	76	126	138	126	*154*	138	138	138	85	138
		76	77	76	138	126	85	76	76	88
		22			76	76	76			

The two aliquots (3948 and 3949) of the same polyclonal cell line, show a similar expression pattern in the gel, although the intensity of the bands are not completely identical, this also indicates that aliquots of the same polyclonal cell line grown under identical conditions will produce anti-RhD rpAb with a similar clonal diversity.

Summary

The present experiment succeeded in generating a library of anti-Rhesus D antibody expression vectors comprising 56 variant anti-Rhesus D-encoding nucleic acid segments (Table 3).

Plasmids containing individual members of the library were used to transfect the CHO-Flp-In (019) cell line, generating 56 individual cell lines capable of expressing a specific anti-RhD antibody.

10 of these cell lines were mixed in order to generate a anti-RhD rpAb manufacturing cell line, which after 9 weeks cultivation still maintained 90% of the initial diversity. After 11 weeks of cultivation mRNA from six different clones could be unambiguously identified and several other clones are likely to be represented in the band an approximately 500 bp.

The fact that two aliquots of the polyclonal CHO-Flp-In (019) cell lines showed similar results with respect to clonal diversity, illustrated that reproducible results can be obtained.

EXAMPLE 2

Generation of a working cell bank for larger scale production

Twenty seven cell cultures were selected to constitute the polyclonal cell line (RhD157.119D11, RhD159.119B09, RhD160.119C07, RhD161.119E09, RhD162.119G12, RhD163.119A02, RhD189.181E07, RhD191.119E08, RhD192.119G06, RhD196.126H11, RhD197.127A08, RhD199.164E03, RhD201.164H12, RhD202.158E07, RhD203.179F07, RhD207.127A11, RhD240.125A09, RhD241.119B05, RhD244.158B10, RhD245.164E06,

RhD293.109A09, RhD301.160A04, RhD305.181E06, RhD306.223E11, RhD307.230E11, RhD319.187A11 and RhD324.231F07).

In addition to the high degree of diversity among the individual clones, the clone selections were also based on growth and production characteristics of the individual cell cultures.

Included in the selection criteria at the cell culture level were:

I. Doubling time; had to be between 24 and 32 hours

II: Intracellular staining; had to show a homogenous cell population

III: Productivity; had to exceed 1.5 pg per cell per day

The 27 different cell cultures will be equally mixed in regard to cell number and this mix will constitute the working cell bank for a pilot plant production of anti-RhD rpAb.

EXAMPLE 3

The present example illustrates the characterization of a polyclonal cell culture with eight members over time. The clonal diversity of the culture was assessed at the genetic level using RFLP analysis and at the protein level using a chromatographic technique in one dimension.

The polyclonal cell line of the present example was constituted of the following eight members: RhD191.119E08, RhD196.126H11, RhD201.164H12, RhD203.179F07, RhD244.158B10, RhD306.223E11, RhD319.187A11 and RhD324.231F07

In the example they will simply be written as follows RhD191, RhD201, RhD203, RhD244, RhD306, RhD319 and RhD324.

RFLP analysis to estimate clone diversity in polyclonal cell cultures

The distribution of the individual clones in a polyclonal cell culture expressing eight different anti-Rhesus D antibodies was estimated by terminal RFLP (T-RFLP) analysis of RT-PCR products derived from the polyclonal cell line. In the T-RFLP procedure the forward and/or reverse primer(s) are fluorescently labeled and therefore a proportion of the restriction fragments generated from the amplicons will contain the label. The labeled fragments can subsequently be separated by capillary electrophoresis and detected by fluorescence. The analysis can be performed both on the light chain and the variable region of the heavy chain-encoding sequences, depending on the primers applied.

Briefly, a cell suspension corresponding to 200 cells was washed one time in PBS and subjected to a freeze-thaw procedure generating lysates used as template in a RT-PCR amplification using a One-Step RT-PCR kit (Qiagen) and suitable primers.

The RT-PCR was carried out on a standard thermal cycler with the following conditions:

Reverse transcription	55 °C for 30 min
Denature	95 °C for 15 min
Start cycle loop (35 cycles)	
Denature	95 °C for 30 sec
Anneal	60 °C for 30 sec
Elongate	72 °C for 5 min
End cycle loop	
Elongate	72 °C for 15 min
Finish	8 °C forever

For analysis of the light chain the following primers were used for the RT-PCR amplification. The reverse primer was 6-carboxyflorescein (FAM) labeled and the primer sequences were as follows:

VL Forward primer: 5'-TCTCTTCCGCATCGCTGTCT
CL Reverse primer: 5'-FAM-AGGAAAGGACAGTGGGAGTGGCAC

Twenty µl of the RT-PCR product was digested with 1 U of *NheI*, 1 U of *PstI* and 1 U of *HinfI* (all from New England Biolabs) in NEB1 for 2 hours.

The labeled fragments were detected by fluorescence capillary electrophoresis on an ABI3700 (Applied Biosystems) at Statens Serum Institute, Copenhagen, DK.

The expected fragments for each of the anti-RhD antibody producing cell clones are shown in Table 6 and the FAM labeled fragments are indicated in bold.

Table 6

RhD #	**191**	**196**	**201**	**203**	**244**	**306**	**319**	**324**
NheI/PstI/HinfI fragment size	**475**	**696**	**516**	**422**	**690**	**682**	**761**	**513**
	210	138	166	318	138	138	138	166
	138	76	138	138	76	76	76	138
	76	67	76	76	67	67	67	76
	67	59	76	67	41	59		76
	58		67	18	18	17		67
	18							

The T-RFLP pattern is shown in Figure 10 and all eight anti-Rhesus D antibody producing clones have been assigned to specific peaks. Under the assumption that there was no template/primer competition during the RT-PCR, the relative peak area will correspond to the relative amount of mRNA transcribed from each antibody light chain gene represented in the polyclonal cell line.

For analysis of the heavy chain variable region within the same polyclonal cell line the RT-PCR amplification was carried out with VH-specific primers. The primer sequences were as follows:

VH Forward primer: 5'-FAM CGTAGCTCTTTTAAGAGGTG
VH Reverse primer: 5'-HEX-ACCGATGGGCCCTTGGTGGA

Twenty µl of the RT-PCR product was digested with 1 U of *RsaI* and 1 U of *NdeI* (all from New England Biolabs) in NEB2 for 2 hours.

The labeled fragments were detected by fluorescence capillary electrophoresis on an ABI3700. The analysis was performed by Statens Serum Institute, Copenhagen, DK.

The expected T-RFLP patterns are shown in Table 7, where the FAM labeled fragments are shown in bold and the HEX (6-Carboxy-2',4,4',5,7,7'-hexachlorofluorescein succinimidyl ester) labeled fragments are underscored.

Table 7

RhD #	**191**	**196**	**201**	**203**	**244**	**306**	**319**	**324**
RsaI/NdeI Fragment size	203	**429**	**186**	**350**	**435**	**328**	232	**266**
	166		142	88		79	**118**	157
	63		79			22	79	
			22			9	9	
			9					

The polyclonal cell line was cultivated over 5 weeks and once a week samples were taken for T-RFLP analyses. The analysis was performed on the variable heavy chain, but could have been performed on the light chain as well if desired.

After capillary electrophoresis of the restriction fragments, the relative peak areas were integrated and used to estimate the clonal diversity of the polyclonal cell culture. The relative quantities over time are shown in Figure 12.

Based on these results, it seems that RhD196 increase whereas RhD203 seems to decrease over time. The quantities of the other clones are quite stable during the cultivation period and all eight cDNA could be detected after five weeks of cultivation.

By performing T-RFLP on both light chain and heavy chain as well as on both mRNA and DNA it should be possible to obtain a precise fingerprint of the clonal diversity within the polyclonal cell culture, for example in cells at the limit of in vitro cell age or at any given time point during cultivation.

The technique can therefore be used to monitor the stability of the clonal diversity in a cell culture over time during antibody production. The technique can also be applied to monitor the batch-to-batch consistency for example of different ampoules frozen down from the same pWCB or in cells harvested after two or more manufacturing runs.

Cation-exchange chromatographic analysis to estimate clonal diversity in a polyclonal cell culture

The polyclonal antibody produced from the same polyclonal cell culture as used in the T-RFLP analysis described above was analyzed using cation-exchange chromatography. The protein A purified recombinantly produced polyclonal antibody was applied onto a PolyCatA column (4.6 x 100 mm) in 25 mM sodium acetate, 150 mM sodium chloride, pH 5.0 at a flow rate of 60 ml h^{-1} operated at room temperature. The antibody components were subsequently eluted using a linear gradient from 150 – 350 mM sodium chloride in 25 mM sodium acetate, pH 5.0 at a flow rate of 60 ml h^{-1}. The antibody components were detected spectrophotometrically at 280 nm and the chromatogram was subsequently integrated and the area of individual peaks was then used to quantitate antibody components. The relative quantities over time are shown in Figure 13.

Summary

The results obtained at the genetic level by the RFLP analysis and at the protein level by cation-exchange chromatography are comparable. Figure 12 and 13 clearly illustrate that most of the individual clones in the polyclonal cell line as well as the individual antibodies of the polyclonal antibody expressed from the cell line follow the same trends during the 5 weeks of cultivation. Thus, analyses at the genetic as well as at protein level are good equivalents for assessing the compositional diversity of a cell line at the genetic level and of the recombinant polyclonal protein produced from the cell line.

EXAMPLE 4

The present example illustrates the characterization of a polyclonal cell culture with twenty-five members over time. The clonal diversity of the culture was assessed at the genetic level

using T-RFLP analysis and at the protein level using a chromatographic technique in one dimension.

The polyclonal cell line of the present example was constituted of the twenty five members indicated in Table 8. Further, the growth characteristics of the individual clones are shown in Table 8.

Table 8

Clone name	Doubling time (h)	Productivity pg/(cell*day)[a]	Clone name	Doubling time	Productivity pg/(cell*day)
RhD157.119D11	25,6	4	RhD207.127A11	34,4	3,8
RhD159.119B09	26,1	1,4	RhD240.125A09	29,6	3,6
RhD160.119C07	25,4	3,8	RhD241.119B05	32,8	4,1
RhD162.119G12	27,7	5,9	RhD245.164E06	28	1,5
RhD189.181E07	27,8	3,2	RhD293.109A09	30,7	7,1
RhD191.119E08	30,8	1,2	RhD301.160A04	29,7	5,1
RhD192.119G06	25,4	1,2	RhD305.181E06	31	6,7
RhD196.126H11	32	8,7	RhD306.223E11	30,9	1,7
RhD197.127A08	30,1	1,6	RhD317.144A02	27	10,4
RhD199.164E03	27,3	2,9	RhD319.187A11	28	5,6
RhD201.164H12	27,6	10,6	RhD321.187G08	31	2,7
RhD202.158E07	28,8	3,1	RhD324.231F07	31,2	6,4
RhD203.179F07	31,5	N.A[c]			

[a] Data represent the average of two ELISA measurements

[b] RhD^{VI} reactive

[c] Data not available

In the following the clone names are generally only identified by their first three digits, e.g. RhD157.119D11 is written as RhD157.

T-RFLP analysis of the variable part of the heavy chain genes derived from a polyclonal cell culture expressing twenty-five different anti-Rhesus D antibodies over a 5 weeks cultivation period.

The polyclonal cell culture examined in the present example was composed of a mixture of cell cultures expressing twenty-five different anti-Rhesus D antibodies (generated as described in Example 1). The polyclonal cell culture was cultivated over 5 weeks and once a week samples were taken for T-RFLP analyses.

The RT-PCR was carried out with the VH-specific primers described in Example 3 and restriction fragmentation was carried out likewise.

T-RFLP of the twenty-five different anti-Rhesus D-encoding sequences will, if all genotypes are present, result in seventeen different FAM labeled fragments. Some fragments will represent up to three different genotypes whereas others will represent a single genotype. The expected sizes of FAM labeled fragments are shown in Table 9 together with the relative quantities of the different FAM labeled fragments over time. Further, one example of a T-RFLP profile is shown in Figure 11.

Table 9

RhD #	RsaI/NdeI FAM fragment size (bp)	Group	Week1 Area %	Week2 Area %	Week3 Area %	Week4 Area %	Week5 Area %
Rhd157	63	1	9.5	5.0	5.3	4.8	4.6
Rhd159	63	1					
Rhd191	63	1					
Rhd319	118	2	0.8	0.2	0.2	0.2	0.0
Rhd201	186	3	1.5	0.8	0.9	1.1	0.7
Rhd192	187	3					
Rhd199	203	4	0.9	0.3	0.3	0.4	0.4
Rhd162	260	5	7.4	3.6	1.7	1.0	0.0
Rhd324	266	6	1.0	0.8	0.6	0.5	0.0
Rhd306	328	7	10.3	8.0	7.2	7.9	7.8
Rhd203	350	8	6.0	3.4	3.8	5.9	8.9
Rhd305	350	8					
Rhd197	356	9	5.1	1.8	1.7	1.8	1.3
Rhd202	359	10	3.8	4.3	5.6	5.2	3.7
Rhd240	369	11	3.3	1.8	1.3	0.8	0.0
Rhd207	414	12	11.7	10.5	10.1	9.9	11.1
Rhd160	426	13	11.3	17.1	17.5	18.1	17.2
Rhd293	426	13					
Rhd196	426	13					
Rhd245	429	14	6.5	7.1	8.3	11.0	16.8
Rhd321	432	15	6.8	9.4	8.3	7.5	4.9
Rhd241	435	16	4.8	13.7	12.5	7.2	4.0
Rhd189	438	17	9.4	12.3	14.8	16.8	18.7
Rhd301	438	17					
Rhd317	438	17					

It was possible to separate the restriction fragments to an extent that allowed information to be obtained for twelve individual clones of the twenty-five clones constituting the cell line.

The remaining fractions could potentially be subjected to sequencing in order to obtain more information on the remaining clones.

Cation-exchange chromatographic analysis to estimate clonal diversity in a polyclonal cell culture expressing twenty-five different anti-Rhesus D antibodies

The polyclonal antibody produced from the same polyclonal cell culture as used in the T-RFLP analysis described above, was analyzed using cation-exchange chromatography. The protein A purified recombinantly produced polyclonal antibody was applied onto a PolyCatA column (4.6 x 100 mm) in 25 mM sodium acetate, 150 mM sodium chloride, pH 5.0 at a flow rate of 60 ml h^{-1} operated at room temperature. The antibody components were subsequently eluted using a linear gradient from 150 – 350 mM sodium chloride in 25 mM sodium acetate, pH 5.0 at a flow rate of 60 ml h^{-1}. The antibody components were detected spectrophotometrically at 280 nm and the chromatogram was subsequently integrated and the area of individual peaks was used to quantitate the different antibody components. Figure 14 shows the chromatogram produced from the sample obtained a week 4, the antibody containing peaks being numbered from 1 to 25. It is pure concurrence that the chromatogram contains an identical number of peaks as the number of individual antibodies in the polyclonal antibody analyzed. Table 10 show the relative content in percent of the total antibody components (AC1 to 25), as well as the representation of the individual antibodies in each antibody component (peak). The assignment of individual antibodies to the integrated chromatographic peaks was based on the retention times and peak patterns obtained from monoclonal antibodies analyzed using cation-exchange chromatography under identical conditions.

Table 10

Peak	RhD# Ab represented	Week 1 Rel.Area %	Week 2 Rel.Area %	Week 3 Rel.Area %	Week 4 Rel.Area %	Week 5 Rel.Area %
AC 1	293, 319	2,06	2,3	1,7	1,06	0,81
AC 2	157, 293	3,63	3,83	3,97	3,89	3,06
AC 3	157, 192	2,66	2,8	2,89	2,83	2,34
AC 4	159, 189, 199	6,11	5,52	5,1	4,1	2,99
AC 5	319	2,18	1,94	1,33	1,08	1,26
AC 6	241, 191	6,01	6,4	6,32	5,42	4,1
AC 7	189, 192, 199, 201	3,89	4,21	3,38	2,95	2,63
AC 8	160	12,1	15,77	18,71	17,59	15,56
AC 9	203, 191	2,65	3,89	3,69	3,99	4,14
AC 10	162, 202	6,78	10,22	13,52	12,29	9,75

Peak	RhD# Ab represented	Week 1 Rel.Area %	Week 2 Rel.Area %	Week 3 Rel.Area %	Week 4 Rel.Area %	Week 5 Rel.Area %
AC 11	203, 306, 301	2,86	3,63	4,35	3,66	3,92
AC 12	245	1,43	1,63	1,5	2,27	2,02
AC 13	301, 321	2,5	3,35	3,92	4,16	3,64
AC 14	305	2,44	2,61	3,12	4,23	6,07
AC 15	196, 197, 240, 305, 321	8,33	7,22	7,36	8,49	4,01
AC 16	197	3,82	2,71	2,15	1,86	7,86
AC 17	196, 240, 324	7,57	5,12	4,86	6,89	7,79
AC 18	197, 321	2,27	1,44	1,51	1,39	2,83
AC 19	196, 240	3,8	2,63	2,87	3,98	6,35
AC 20	317	4,58	1,39	0,77	0,71	0,86
AC 21	317	2,86	0,59	0,36	0,83	0,42
AC 22	207	2,07	2,61	1,58	1,65	1,93
AC 23	207	3,33	3,87	2,56	2,41	2,87
AC 24	207	2,46	3,48	1,73	1,52	1,92
AC 25	Unknown	1,58	0,83	2	0,75	0,87

Cation-exchange chromatography separates individual antibody members from a polyclonal antibody based on differences in net charge between the individual members and in addition separates forms of individual antibodies that appear charge heterogeneous. Several antibodies were therefore represented in a single peak, e.g. AC 1 containing RhD293 and RhD319 (see Table 10) and some individual antibodies were further represented in several chromatographic peaks, e.g. RhD319 which is present both in AC1 and 5 (see Table 10).

Peaks which contain more than one individual antibody could be subjected to additional protein chemical characterization techniques, such as quantitative analysis with anti-idiotype peptides, proteolytic peptide mapping, N-terminal sequencing or a second dimension chromatography.

Summary

The present example illustrates the combined use of T-RFLP analyses and cation-exchange chromatography for assessing the distribution of the primary transcripts and of antibody components, respectively, over a period of cultivation. The T-RFLP analysis allows for unique identification of 12 individual clones of the 25 clones expressed in the polyclonal cell line and in the present example it is illustrated that these 12 clones could be detected during 4 weeks

cultivation with the T-RFLP analysis. Potentially, more clones could be identified by sequence analysis of fragments representing more than one clone. The distribution of antibody components was analyzed using cation-exchange chromatography and in the present example it is seen that the distribution of the 25 analyzed components is relatively stable during cultivation Although unique identification of all individual antibodies is difficult due to the inherent charge heterogeneous nature of the expressed antibodies it was demonstrated in the present example that antibody component 8 representing the RhD160 antibody showed the highest antibody level during the cultivation period in accordance with the high T-RFLP values obtained for group 13 representing the RhD160, 293, and 196 clones. Furthermore, the RhD 207 component, which could be uniquely identified by T-RFLP as well as by cation-exchange chromatography, showed T-RFLP levels of 10-11% and slightly lower levels of 5.5-10% obtained at antibody level. Overall, the two techniques together demonstrate a relatively stable production at the mRNA and antibody level during cultivation; however, potential discrepancies between the two techniques could also be seen, illustrated by the apparent loss of transcription of some clones at weeks 5 of cultivation contrasting the results obtained at the antibody level. Thus, the present example justifies the complementary use of both techniques to define cultivation intervals within which stable production of complex polyclonal protein can be obtained.

EXAMPLE 5

The present example demonstrates the generation of pWCB containing anti-RhD rpAb with 25 individual members and provides confirmation of a minimal batch-to-batch variation of rpAb products purified from different vials from the pWCB.

Generation of the pWCB

To generate a pWCB containing anti-RhD rpAb with 25 individual members, one vial of each of 25 banked monoclonal anti-RhD antibody production cell lines (RhD157, 159, 160, 162, 189, 191, 192, 196, 197, 199, 201, 202, 203, 207, 240, 241, 245, 293, 301, 305, 306, 317, 319, 321, 324) were thawed in ExCell 302 medium containing 4 mM glutamine and expanded for 3 weeks in the same medium supplemented with 500 μg/ml G418 and anti-clumping agent diluted 1:250. Equal numbers of cells (2×10^6) from each culture were then carefully mixed together, and frozen in liquid nitrogen (5×10^7 cells/vial) using standard freezing procedures.

Cultivation in bioreactors

Vials from the pWCB were thawed in T75 flasks (Nunc, Roskilde, Denmark) and expanded in spinner flasks (Techne, Cambridge, UK). 5 L bioreactors (Applikon, Schiedam, Netherlands) were inoculated with 0.6×10^6 cells/ml in 1.5 L. During the reactor runs, cells were fed on a

daily basis with ExCell 302 medium supplemented with concentrated feed solution, glutamine and glucose to a final volume of 4.5 L. The bioreactor runs were terminated after 16-17 days. The three batches are termed Sym04:21, Sym04:23 and Sym04:24. The batches were cultured at different points in time.

Analysis of batch-to-batch variation

The recombinant polyclonal antibody samples were purified by affinity chromatography using HiTrap™ rProtein A columns (GE Healthcare, UK).

The purified recombinant polyclonal antibody samples were analyzed using cation-exchange chromatography employing a PolyCAT A column (4,6 x 100 mm, from PolyLC Inc., MA, US) in 25 mM sodium acetate, 150 mM sodium chloride, pH 5.0 at a flow rate of 60 ml/h (room temperature). The antibody peaks were subsequently eluted using a linear gradient from 150 mM to 350 or 500 mM NaCl in 25 mM sodium acetate, pH 5.0 at a flow rate of 60 ml/h. The antibody peaks were detected spectrophotometrically at 280 nm. The chromatograms were integrated and the area of individual peaks used for quantification. As already mentioned some of the individual antibodies displayed charge heterogeneity and two antibodies may contribute to the same peak in the IEX chromatogram.

Table 11 show the relative content in percent of the total antibody components (AC). In the present example the relative area has been calculated for 35 AC, whereas Example 4 only calculated the relative area for 25 AC. This difference is strictly due to a different assignment of the peaks in the chromatogram and not to actual differences in the profile as such.

Table 11

Peak	Average Rel.Area %	Standard deviation	Peak	Average Rel.Area %	Standard deviation
AC 1	1,71	0,35	AC 19	1,79	0,16
AC 2	2,36	0,13	AC 20	1,39	0,07
AC 3	4,40	0,78	AC 21	1,32	0,15
AC 4	3,58	0,78	AC 22	2,60	0,23
AC 5	5,83	0,60	AC 23	1,59	0,25
AC 6	2,11	0,25	AC 24	0,62	0,12
AC 7	4,16	0,33	AC 25	1,12	0,06
AC 8	4,21	0,59	AC 26	1,31	0,04
AC 9	3,41	0,97	AC 27	0,58	0,12
AC 10	14,22	2,91	AC 28	1,30	0,25
AC 11	4,24	0,79	AC 29	1,05	0,39
AC 12	2,98	0,47	AC 30	0,66	0,24
AC 13	2,31	0,16	AC 31	0,70	0,44
AC 14	2,44	0,26	AC 32	1,64	0,10

Peak	Average Rel.Area %	Standard deviation	Peak	Average Rel.Area %	Standard deviation
AC 15	9,17	0,52	AC 33	2,30	0,16
AC 16	5,08	0,43	AC 34	1,77	0,24
AC 17	1,98	0,26	AC 35	1,03	0,44
AC 18	3,04	0,26			

Table 11 shows that the reproducibility between the harvested antibody products from the three batches was high. The variation in the size of individual antibody peaks was within 20% for most antibody components, whereas the variation for some of the smallest peaks was slightly larger.

EXAMPLE 6

The present example demonstrates that different batches of an anti-RhD rpAb with 25 individual members (same composition as in Example 4) bind to RhD-positive erythrocytes with similar potency and show comparable biological activity with respect to the relevant effector mechanisms: Antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis.

Preparation of red blood cells

Red blood cells (RBC) were prepared from whole blood obtained from healthy donors after informed consent at the Blood Bank, Aalborg Hospital, DK, by washing the blood three times in PBS (Gibco, Invitrogen, United Kingdom) containing 1 % bovine serum albumin (BSA, Sigma-Aldrich, Germany). The erythrocytes were resuspended and stored at 4°C as a 10% solution in ID-Cellstab (DiaMed, Switzerland).

Preparation of PBMC

Buffy coats containing blood from healthy donors were obtained from the Blood Bank at the National Hospital, Copenhagen, Denmark and peripheral blood mononuclear cells (PBMC) were purified on Lymphoprep (Axis-Shield, Norway).

Potency assay

The potency assay was adopted from the European Pharmacopoeia 4 (section 2.7.13 method C). The binding capacity of an anti-RhD rpAb with 25 individual members was measured using RhD-positive erythrocytes at 5 x 10^4 cells/µl in PBS, 1% BSA. Anti-RhD rpAb batches, Sym04:21, Sym04:23, and Sym04:24, were obtained from individual 5 L fed batch bioreactor runs. Dilutions (1½-fold) of the Anti-RhD rpAb batches were made in PBS, 1% BSA in triplicate in 96 well plates (Becton Dickinson Labware, NJ, USA). Fifty µl of the anti-RhD rpAb dilutions were mixed with 50 µl of erythrocytes and incubated at 37°C for 40 min. The

cells were washed twice (300xg, 2 min) in PBS, 1% BSA. Eighty µl of phycoerythrin-conjugated goat anti-human IgG, (Beckman Coulter, CA, USA) diluted 1:20 in PBS, 1% BSA was added to each sample and left at 4°C for 30 min. The samples were washed in PBS, 1% BSA and in FacsFlow (Becton Dickinson, Belgium) (300xg, 2 min), and resuspended in 200 µl FACSFlow. The samples were run on a FACSCalibur (Becton Dickinson, CA, USA) and data analysis performed using CellQuest Pro and Excel. The three individual Anti-RhD rpAb batches displayed essentially identical binding potency to RhD-positive erythrocytes (Fig. 15A)

Combined ADCC and phagocytosis assay

This assay was adapted from Berkman et al. 2002. Autoimmunity 35, 415-419. Briefly, RhD positive (RhD+) and RhD negative (RhD-) red blood cells (RBC) were labeled with radioactive Chromium. For Cr^{51} labeling, 1 x 10^8 RhD+ and RhD- RBC, respectively, were centrifuged (600xg for 10 min) and 100 µl Dulbeccos' modified eagles medium (DMEM) and 200 µl sodium chromate (0.2 µCi) (GE Healthcare, UK) were added to each tube before incubation for 1.5 hours at 37°C. The suspension was washed twice in 50 ml PBS and resuspended in 1 ml complete DMEM (containing 2 mM glutamine, 1% Penicillin-Streptomycin and 10% fetal calf serum) (Invitrogen, CA, US). Cells were adjusted to 4 x 10^6 cells/ml and 50 µl/well were added to 96-well cell culture plates (Nunc). Fifty µl of two-fold dilutions of Anti-RhD rpAb from batch Sym04:21 or Sym04:24, was then added to each well, except control wells. Control wells were supplied with complete DMEM and used for either spontaneous lysis/retention or maximum lysis.

The PBMC were adjusted to 2 x 10^7 cells/ml, and 100 µl were added to each well and incubated at 37°C overnight. One hundred µl 1% Triton-X-100 (Merck, Germany) was added to the maximum lysis control wells. The plates were centrifuged (600xg for 2 min) and 50 µl of the supernatant was transferred to ADCC Lumaplates (Perkin Elmer, Belgium).

Following transfer of the supernatants, the cell culture plates were centrifuged (300xg for 2 min) and 50 µl supernatant from the maximum lysis wells were transferred to another LumaPlate (phagocytosis LumaPlate). In the cell culture plate, the supernatant was removed from the remaining wells and lysis buffer (140 mM NH_4Cl, 17 mM Tris-HCl) was added, followed by 5 min incubation at 37°C. NH_4Cl lyses the RBC, but leaves the PBMC fraction and thereby the phagocytozed RBC intact. After RBC lysis, the plates were centrifuged (4°C, 2 min, 300 g), pellets were washed twice in PBS, and resuspended in 100 µl PBS. One hundred µl 1% Triton-X-100 was added to the wells to lyse the phagocytic PBMC, and 50 µl of the lysate was transferred to the phagocytosis LumaPlates. The Lumaplates were dried overnight at 40°C and counted in a TopCount NXT (Packard, CT, USA). All data were imported into

Excell and analyzed as described by Berkman et al. 2002. Autoimmunity 35, 415-419. Briefly, the computations were performed as follows:

ADCC: Immune lysis (%)
= (mean test Cr^{51} released – mean spontaneous Cr^{51} released) / (total Cr^{51} in target erythrocytes- machine background) x 100

Phagocytosis: Immune phagocytosis (%)
= (mean test Cr^{51} retention – mean spontaneous Cr^{51} retention) / (total Cr^{51} in target erythrocytes- machine background) x 100

All data were normalized to the combined maximum plateau values

The functional activity of anti-RhD rpAb from the two consecutive reactor runs showed nearly identical functional activity in both *in vitro* assays (Fig. 15B and 15C) reflecting the high consistency between the batches.

EXAMPLE 7

The present example demonstrates that the clonal diversity of an anti-RhD rpAb with 25 individual members (same composition as in Example 4) is maintained during down-stream processing (DSP). Cation-exchange chromatographic analysis is used to estimate clonal diversity during DSP of the recombinant polyclonal antibody.

Down-stream processing

An anti-RhD rpAb sample, containing 25 individual members, from a developmental bioreactor run was purified using the following DSP steps:

1. capture of the antibodies using a MAbSelect column
2. virus inactivation at pH 3
3. buffer exchange using a Sephadex G-25 column
4. anion-exchange chromatography using a DEAE-Sepharose column
5. virus filtration using a Planova 15N filter, and
6. hydrophobic charge induction chromatography using a MEP Hypercel column
7. ultra filtration/diafiltration using a Millipore biomax filter

Analysis of clonal diversity after individual DSP steps

Cation-exchange chromatography was used to analyze the clonal diversity during DSP of a recombinant polyclonal antibody composition. Samples taken after step 1, 3, 4 and 6 during DSP of a anti-RhD rpAb was applied onto a PolyCatA column (4.6 x 100 mm) in 25 mM sodium acetate, 150 mM sodium chloride, pH 5.0 at a flow rate of 60 ml h-1 operated at room temperature. The antibody components were subsequently eluted using a linear

gradient from 150 – 500 mM sodium chloride in 25 mM sodium acetate, pH 5.0 at a flow rate of 60 ml h-1. The antibody components were detected spectrophotometrically at 280 nm and the chromatograms were compared (Fig. 16) to detect the potential loss of clonal diversity during DSP. In the present example it was demonstrated, using cation-exchange chromatography that the clonal diversity is essentially unchanged during DSP of a recombinant polyclonal antibody.

Claims

1. A method for generating a collection of cells suitable as manufacturing cell line for expression of an anti-RhD recombinant polyclonal antibody, said method comprising:

a) providing a library of anti-RhD antibody expression vectors, wherein each individual vector of said library comprises 1) one single copy of a nucleic acid segment encoding a distinct member of the anti-RhD polyclonal antibody and 2) one or more recombinase recognition sequences;

b) introducing said library of anti-RhD antibody expression vectors into a host cell line, wherein the genome of each individual cell of said host cell line comprises a recombinase recognition sequence(s), matching that of the vector, in its genome;

c) ensuring the presence in said cells of one or more recombinases so that the anti-RhD antibody-encoding nucleic acid segments of step (a) are integrated site-specifically in the cells of the host cell line, where said recombinase(s) is/are either i) expressed by said cells into which said nucleic acid segment is introduced; ii) operatively encoded by the vectors of step (a); iii) provided through expression from a second vector; or iv) provided to the cell as a protein; and

d) selecting cells comprising an integrated copy of the anti-RhD antibody-encoding nucleic acid segment from said library of anti-RhD antibody expression vectors.

2. The method according to claim 1, wherein said library of anti-RhD antibody expression vectors is introduced into said host cell line by transfecting said host cells separately with individual members of said library of vectors, and said cells are pooled to form a collection of cells suitable as a recombinant polyclonal manufacturing cell line subsequent to the selection of step (d).

3. The method according to claim 1, wherein said library of anti-RhD antibody expression vectors is introduced into said host cell line by semi-bulk transfection of aliquots of said host cells with fractions comprising 5 to 50 individual vectors of said library of vectors, and said cells are pooled to form a collection of cells suitable as a recombinant polyclonal manufacturing cell line subsequent to the selection of step (d).

4. The method according to claim 1, wherein said library of anti-RhD antibody expression vectors is introduced into said host cell line by bulk transfection of a collection of said host cells with said library of vectors.

5. The method according to any one of the preceding claims, wherein the library of anti-RhD antibody expression vectors encodes an anti-RhD recombinant polyclonal antibody where at least one of the individual members specifically bind to epD3, epD4 and epD9 (RhD category VI antigen) and further members alone or in combination bind to the remaining Rhesus D antigen epitopes epD1, epD2, epD5, epD6/7 and epD8.

6. The method according to any one of the preceding claims, wherein said library of anti-RhD antibody expression vectors comprise variant nucleic acid segments each comprising CDR1, CDR2 and CDR3 regions selected from one of the V_H:LC pairs corresponding to the pairs of nucleic acid sequences identifiable by the distinct clone names in table 3.

7. The method according to claim 6, wherein the CDR1, CDR2 and CDR3 regions from the V_H:LC pairs are identified by clone names RhD157.119D11, RhD158.119B06, RhD159.119B09, RhD161.119E09, RhD163.119A02, RhD190.119F05, RhD191.119E08, RhD192.119G06, RhD197.127A08 and RhD204.128A03.

8. The method according to claim 6, wherein the CDR1, CDR2 and CDR3 regions from the V_H:LC pairs are identified by clone names RhD157.119D11, RhD159.119B09, RhD160.119C07, RhD162.119G12, RhD189.181E07, RhD191.119E08, RhD192.119G06, RhD196.126H11, RhD197.127A08, RhD199.164E03, RhD201.164H12, RhD202.158E07, RhD203.179F07, RhD207.127A11, RhD240.125A09, RhD241.119B05, RhD245.164E06, RhD293.109A09, RhD301.160A04, RhD305.181E06, RhD306.223E11, RhD317.144A02, RhD319.187A11, RhD321.187G08 and RhD324.231F07.

9. The method according to any one of the preceding claims, wherein said single copy of a nucleic acid segment encoding a distinct member of the anti-RhD polyclonal, is integrated in a single predefined genomic locus of each individual cell in said collection of cells, said locus being capable of mediating high-level expression of each member of said recombinant polyclonal antibody.

10. The method according to any one of the preceding claims, wherein said collection of cells is derived from a mammalian cell line or cell type.

11. The method according to claim 10, wherein said mammalian cell line is selected from the group consisting of Chinese hamster ovary (CHO) cells, COS cells, BHK cells, YB2/0, NIH 3T3, myeloma cells, fibroblasts, HeLa, HEK 293, PER.C6, and cell lines derived thereof.

12. A method for generating a polyclonal working cell bank, said method comprising:

a) providing a collection of cell lines, obtained from host cells which have been individually transfected with an individual member of a library comprised of variable region-encoding nucleic acid segments, and where each individual cell line upon transfection produces a different member of a polyclonal protein,

b) mixing a predefined number of cells expanded from each of said cell lines, and

c) freezing aliqouts of the mixture.

13. The method according to claim 12, wherein an aliquot obtained in step c) is thawn and expanded for a number of generations sufficient to produce a total number of cells, which are

frozen down in a new series of aliquots (a sub-pWCB), with approximately the same number of cells in each aliquot of said sub-pWCB as in said thawn aliquot.

14. The method according to claim 12 or 13, wherein said library comprised of variable region-encoding nucleic acid segments is a library comprised of antibody V_H and V_L-encoding nucleic acid segments.

15. The method according to claim 14, wherein said library comprised of antibody VH and VL-encoding nucleic acid segments encodes an anti-RhD recombinant polyclonal antibody.

16. The method according to any one of the claims 12 to 15, wherein said individual cell lines are selected, prior to the mixing of the cells, such that they have similar proliferation rates and/or productivity.

17. The method according to claim 16, wherein said individual cell lines are selected for similar productivity by FACS analysis.

18. The method according to claim 16, wherein said individual cell lines are selected for similar productivity and/or proliferation rates by means of a robot.

19. The method according to any one of the claims 16 to 18, wherein said selected cell lines have a proliferation rate between 22 and 40 hours and/or a productivity exceeding 1.5 pg/(cell*day).

20. The method according to any one of the claims 12 to 19, wherein said individual cell lines are cloned cell lines.

21. The method according to any one of the claims 12 to 20, wherein each individual cell line produces a full-length antibody with properties that differ from the properties of the antibodies produced by the other members of the polyclonal working cell bank.

22. The method according to any one of the claims 12 to 21, wherein said individual cell lines are mixed at equal ratios

23. The method according to any one of the claims 12 to 21, wherein said individual cell lines are mixed at different ratios.

24. The method according to claim 23, wherein the ratio of one or more individual cell lines producing an antibody which binds a particular antigen is increased compared to the other members of the polyclonal working cell bank.

25. The method according to claim 23, wherein the ratio of one or more individual cell lines characterized by having a slower proliferation rate is increased compared to other members of the polyclonal working cell bank characterized by a faster proliferation rate.

26. A polyclonal working cell bank comprising a mixture of a predefined number of cells from a collection of individual cell lines, where each individual cell line is obtained from host cells which have been individually transfected with an individual member of a library comprised of variable region-encoding nucleic acid segments, and where each individual cell line produces a different member of a polyclonal protein, and where said pWCB has been frozen down in aliquots.

27. The polyclonal working cell bank according to claim 26, wherein said individual cell lines have similar proliferation rates and/or productivity.

28. The polyclonal working cell bank according to claim 26 or 27, wherein said individual cell lines are cloned cells.

29. The polyclonal working cell bank according to any one of the claims 26 to 28, wherein said individual cell lines are mixed at different ratios.

30. A method for the manufacture of an anti-RhD recombinant polyclonal antibody, said method comprising:

a) providing a polyclonal working cell bank according claim 15 or claims 16 to 25 as dependent on claim 14, or providing a collection of cells comprising a library of variant anti-RhD antibody-encoding nucleic acid segments, wherein each individual cell in said collection contains a single copy of a nucleic acid segment encoding a distinct member of said anti-RhD polyclonal antibody, said copy being integrated at the same site of the genome of each individual cell;

b) culturing said polyclonal working cell bank or collection of cells under conditions facilitating expression of said recombinant polyclonal antibody; and

c) recovering said expressed recombinant polyclonal antibody from the cell culture, cells or supernatant.

31. The method according to claim 30, wherein the recovered recombinant polyclonal antibody is subjected to further purification.

32. The method according to claims 30 or 31, wherein the collection of cells in step (a) is generated according to the method of any one of claims 1-11.

33. A library of anti-RhD expression vectors for site-specific integration comprising a population of variant anti-RhD antibody-encoding nucleic acid segments, wherein each of said vectors comprises 1) one copy of a nucleic acid segment encoding a distinct member of the anti-RhD polyclonal antibody and 2) one or more recombinase recognition sequences.

34. The library according claim 33, wherein at least one of the individual members of said population of variant anti-RhD antibody-encoding nucleic acid segments encodes an anti-RhD antibody that specifically bind to epD3, epD4 and epD9 (RhD category VI antigen) and further members alone or in combination bind to the remaining Rhesus D antigen epitopes epD1, epD2, epD5, epD6/7 and epD8.

35. The library according to claim 33 or 34, wherein said library comprise variant nucleic acid segments each comprising CDR1, CDR2 and CDR3 regions selected from one of the V_H:LC pairs corresponding to the nucleic acid sequences identifiable by the distinct clone names in table 3.

36. The library according to claim 35, wherein the CDR1, CDR2 and CDR3 regions from the V_H:LC pairs are identified by clone names RhD157.119D11, RhD158.119B06, RhD159.119B09, RhD161.119E09, RhD163.119A02, RhD190.119F05, RhD191.119E08, RhD192.119G06, RhD197.127A08 and RhD204.128A03.

37. The library according to claim 35, wherein the CDR1, CDR2 and CDR3 regions from the V_H:LC pairs are identified by clone names RhD157.119D11, RhD159.119B09, RhD160.119C07, RhD162.119G12, RhD189.181E07, RhD191.119E08, RhD192.119G06, RhD196.126H11, RhD197.127A08, RhD199.164E03, RhD201.164H12, RhD202.158E07, RhD203.179F07, RhD207.127A11, RhD240.125A09, RhD241.119B05, RhD245.164E06, RhD293.109A09, RhD301.160A04, RhD305.181E06, RhD306.223E11, RhD317.144A02, RhD319.187A11, RhD321.187G08 and RhD324.231F07.

38. A library of anti-RhD antibody-encoding nucleic acid segments, where each segment comprise CDR1, CDR2 and CDR3 regions selected from one of the V_H:LC pairs corresponding to the pairs of nucleic acid sequences identifiable by a distinct clone name of table 3.

39. The library to claim 38, wherein the CDR1, CDR2 and CDR3 regions from the V_H:LC pairs are identified by clone names RhD157.119D11, RhD158.119B06, RhD159.119B09, RhD161.119E09, RhD163.119A02, RhD190.119F05, RhD191.119E08, RhD192.119G06, RhD197.127A08 and RhD204.128A03.

40. The library according to claim 38, wherein the CDR1, CDR2 and CDR3 regions from the V_H:LC pairs are identified by clone names RhD157.119D11, RhD159.119B09, RhD160.119C07, RhD162.119G12, RhD189.181E07, RhD191.119E08, RhD192.119G06, RhD196.126H11, RhD197.127A08, RhD199.164E03, RhD201.164H12, RhD202.158E07, RhD203.179F07, RhD207.127A11, RhD240.125A09, RhD241.119B05, RhD245.164E06, RhD293.109A09, RhD301.160A04, RhD305.181E06, RhD306.223E11, RhD317.144A02, RhD319.187A11, RhD321.187G08 and RhD324.231F07.

41. A recombinant polyclonal manufacturing cell line comprising a collection of cells transfected with a library of anti-RhD antibody-encoding nucleic acid segments, wherein each cell in said collection is capable of expressing one member of the library, which encodes a distinct member of an anti-RhD recombinant polyclonal antibody and which is located at the same site in the genome of individual cells in said collection, wherein said nucleic acid segment is not naturally associated with said cell in the collection.

42. The recombinant polyclonal manufacturing cell line according to claim 41, wherein said nucleic acid segment encoding a distinct member of the anti-RhD polyclonal, is integrated in a single predefined genomic locus of each individual cell in said collection of cells, said locus being capable of mediating high-level expression of each member of said recombinant polyclonal antibody.

43. The recombinant polyclonal manufacturing cell line according to claim 41 or 42, wherein said collection of cells is derived from a mammalian cell line or cell type.

44. The recombinant polyclonal manufacturing cell line according to claim 43, wherein said mammalian cell line is selected from the group consisting of Chinese hamster ovary (CHO) cells, COS cells, BHK cells, YB2/0, NIH 3T3, myeloma cells, fibroblasts, HeLa, HEK 293, PER.C6, and derivative cell lines thereof.

45. The recombinant polyclonal manufacturing cell line according to any of the claims 41 to 44, wherein said library is a library according to one of the claims 33 to 3740

46. An anti-RhD recombinant polyclonal antibody obtained by the method according to claims 30 or 32.

47. An anti-RhD recombinant polyclonal antibody where each individual member comprises CDR1, CDR2 and CDR3 regions selected from one of the V_H:LC pairs corresponding to the pairs of amino acid sequences identifiable by a distinct clone name in table 3.

48. The anti-RhD recombinant polyclonal antibody according to claim 46 or 47, where at least one of the individual members specifically bind to epD3, epD4 and epD9 (RhD category

VI antigen) and further members alone or in combination bind to the remaining Rhesus D antigen epitopes epD1, epD2, epD5, epD6/7 and epD8.

49. The anti-RhD recombinant polyclonal antibody according to claim 47 or 48, wherein the CDR1, CDR2 and CDR3 regions from the V_H:LC pairs are identified by clone names RhD157.119D11, RhD158.119B06, RhD159.119B09, RhD161.119E09, RhD163.119A02, RhD190.119F05, RhD191.119E08, RhD192.119G06, RhD197.127A08 and RhD204.128A03.

50. The anti-RhD recombinant polyclonal antibody fragment according to claim 47 or 48, wherein the CDR1, CDR2 and CDR3 regions from the V_H:LC pairs are identified by clone names RhD157.119D11, RhD159.119B09, RhD160.119C07, RhD161.119E09, RhD162.119G12, RhD163.119A02, RhD189.181E07, RhD191.119E08, RhD192.119G06, RhD196.126H11, RhD197.127A08, RhD199.164E03, RhD201.164H12, RhD202.158E07, RhD203.179F07, RhD207.127A11, RhD240.125A09, RhD241.119B05, RhD244.158B10, RhD245.164E06, RhD293.109A09, RhD301.160A04, RhD305.181E06, RhD306.223E11, RhD307.230E11, RhD319.187A11 and RhD324.231F07.

51. A method for treatment, amelioration or prophylaxis in an animal, wherein an effective amount of the anti-RhD recombinant polyclonal according to one of the claims 46 to 50 is administered.

52. Use of an anti-RhD recombinant polyclonal antibody according to one of the claims 46 to 50 for the preparation of a composition for the prophylaxis of hemolytic disease of the newborn, treatment of idiopathic thrombocytopenic purpura (ITP), or prevention of sensitization to the Rhesus D antigen after mistransfusions of RhD(+) blood to RhD(-) individuals.

53. A pharmaceutical composition comprising as an active ingredient, an anti-RhD recombinant polyclonal antibody according to claim one of the claims 46 to 50 and a pharmaceutically acceptable excipient.

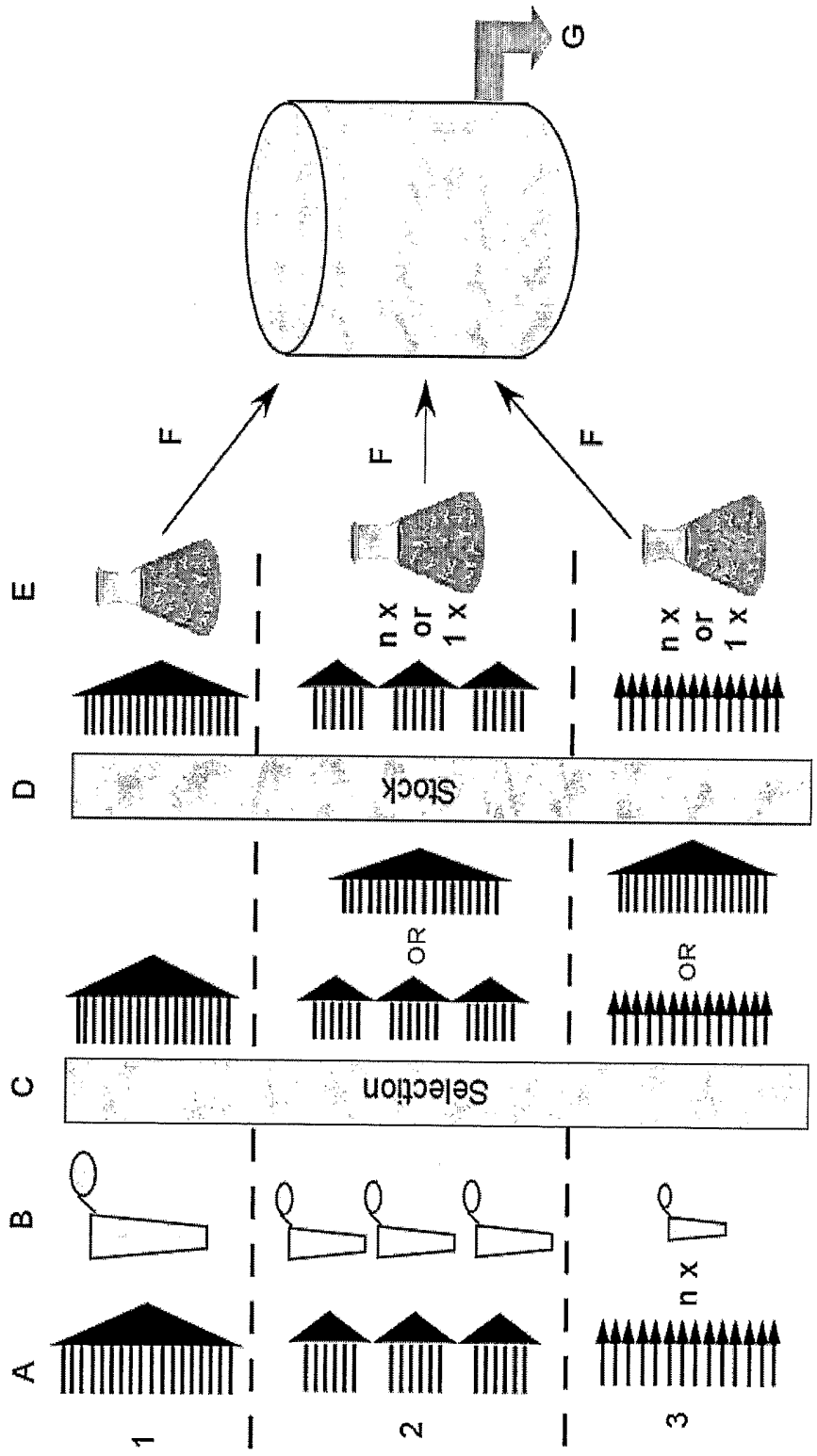
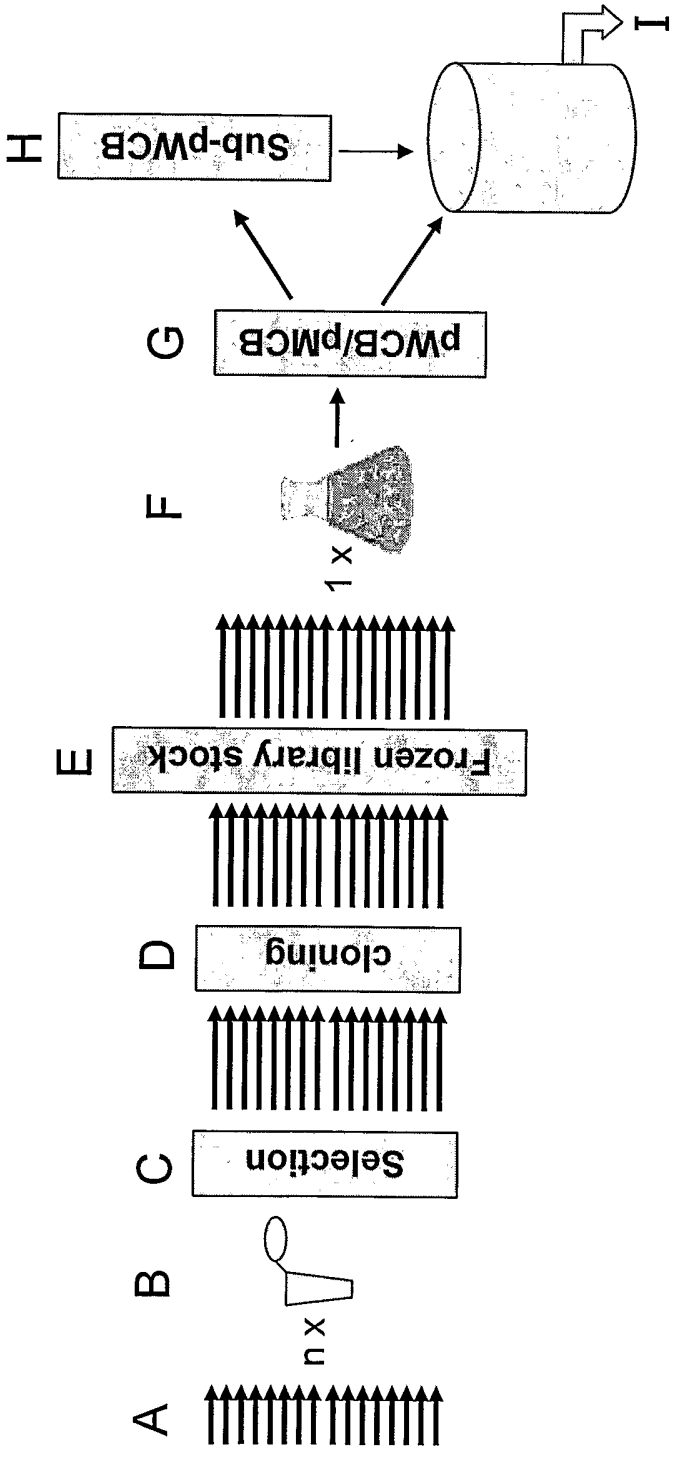


Fig. 1A


A
n x
B
Selection
C
cloning
D
Frozen library stock
E
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F
pWCB/pMCB
G
Sub-pWCB
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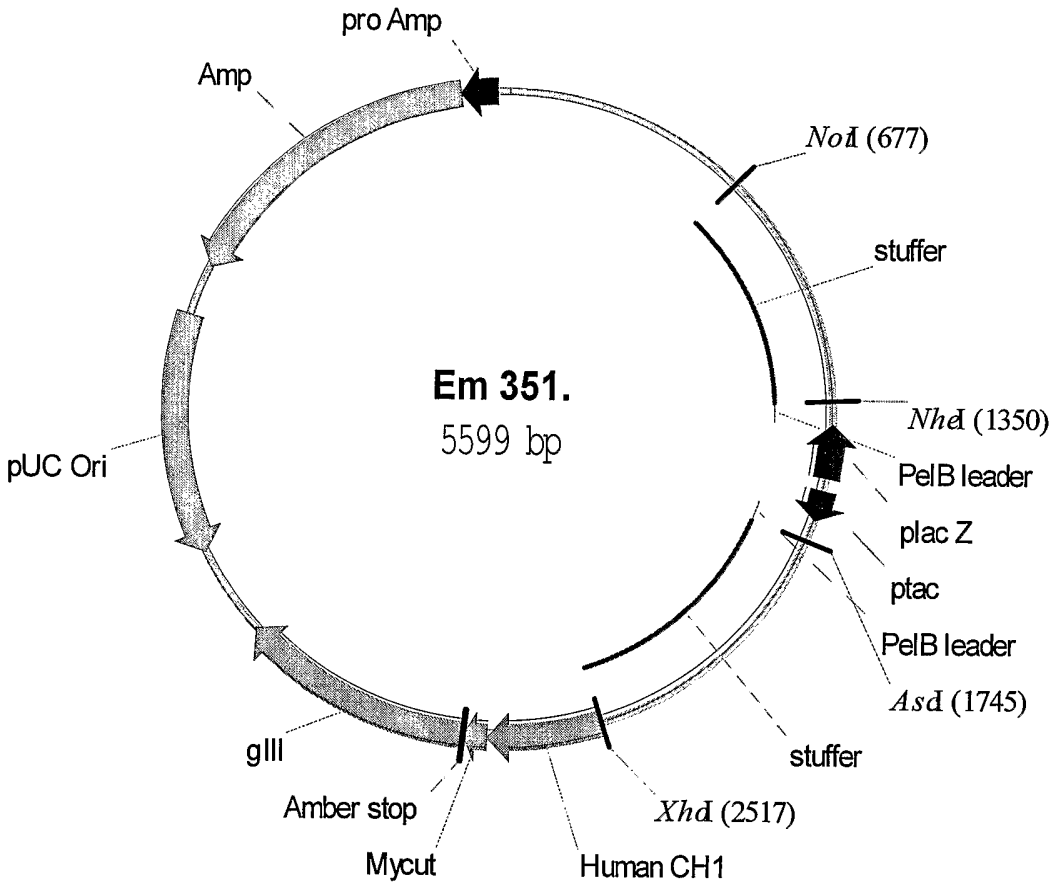
Fig. 1B

Fig. 2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Amp
NotI (677)
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NheI (1350)
pUC Ori
PelB leader
plac Z
ptac
PelB leader
AsdI (1745)
gIII
stuffer
Amber stop
XhoI (2517)
Mycut
Human CH1

Fig. 3A


```
                                                                                                                          CDR1
                               1                                                                                     ---------------------      135
RhD157.119D11 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCTTGGTACAGCCTGGAGGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGATTCACCTTCAG------GAGTTTTGACATGAACTGGGTCCGCCAGGCTCCAGGG
RhD295.119B11 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCTTGGTACAGCCTGGAGGGTCCCTGAGACTCTCCTGTGTAGGCTCTGGATTCACCTTCAG------GAGTTTTGATATGAACTGGGTCCGCCAGGCTCCAGGG
RhD191.119E08 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GACCTGGTACAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAG------GAGTTATGAAATGAACTGGGTCCGCCAGGCTCCAGGG
RhD159.119B09 Vheavy      (1) GAGGTGCAGCTGGTGGAGACCGGGGGA---GGCTTAGTACAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGCTTCAG------GAGTTATGACATGAACTGGGTCCGCCAGGCTCCAGGG
RhD162.119G12 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCCTGGTCAAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCGGCTTCAG------TGCTTATAGCATGAACTGGGTCCGCCAGGCTCCGGGG
RhD205.160B12 Vheavy      (1) GAGGTGCAGCTGGTGGAGACCGGGGGA---GGCCTGGTCAAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAG------GAGTTATAGCATGAACTGGGTCCGCCAGGCTCCAGGG
RhD321.187G08 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCCTGGTCAAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAG------GAGTTATAGCATGAACTGGGTCCGCCAGGCTCCAGGG
RhD192.119G06 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCCTGGTCAAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAG------TAGTTATGCCATGAACTGGGTCCGCCAGGCTCCAGGG
RhD163.119A02 Vheavy      (1) CAGGTGCAGCTGCAGGAGTCGGGCCCA---GGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAG------TAGTTACTACTGGAGCTGGGTCCGGCAGCCCCCAGGG
RhD241.119B05 Vheavy      (1) CAGGTGCAGCTGCAGGAGTCGGGCCCA---GGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCATCTGCACTGTCTCTGGTGGCTCCATCAG------TAGTAACTACTGGAGCTGGATCCGGCAGCCCCCAGGG
RhD195.127A07 Vheavy      (1) CAGGTGCAGCTGCAGGAGTCGGGCCCA---GGACTGGTGAAGCCTTCACAGACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTAGTTACTACTGGAGCTGGATCCGGCAGCCCGCCGGG
RhD240.125A09 Vheavy      (1) CAGCTGCAGCTGCAGGAGTCGGGCCCA---GGACTGGTGAAGCCTTCGGGGACCCTGTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATGAGGAG---TAGTAACTGGTGGACTTGGGTCCGCCAGCCCCCAGGG
RhD317.144A02 Vheavy      (1) CAGGTGCAGCTGCAGGAGTCCGGCCCA---GGACTGGTGAAGCCTTCGGGGACCCTGTCCCTCACCTGCGCTGTCTCTGGTGGCTCCATCAGGGG---TAGTAATTGGTGGAGTTGGGTCCGCCAGCCCCCAGGG
RhD194.126G10 Vheavy      (1) CAGGTCACCTTGAAGGAGTCTGGTCCT---GTGCTGGTGAAACCCACAGAGACCCTCACGCTGACCTGCACCGTCTCTGGGTTCTCACTCAGCAATGCTAGAATGGGTGTGAGCTGGATCCGTCAGCCCCCAGGG
RhD324.231F07 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCTTAGTTCAGCCGGGGAGGTCCCTGAGACTCTCCTGTGTAGCCTCTGGATTCACCTTCAG------TAGCTACTGGATGCACTGGGTCCGCCAAGTTCCAGGG
RhD244.158B10 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCTCTGAGACTCTCCTGTGCAGCCTCGGGATTCAGCTTCAG------TAGTTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD158.119B06 Vheavy      (1) GAGGTGCAGCTGGTGGAGACCGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCTCCTTCAG------TAACTTTGGCTTCCACTGGATCCGCCAGTCTCCAGGC
RhD160.119C07 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAATTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD161.119E09 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGTCTGGGAGGTCCCTGAGACTCTCATGTGCAGCCTCTGGATTCACCTTCAG------TAACAATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD190.119F05 Vheavy      (1) GAGGTGCAGCTGGTGGAGACCGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGCTTCAG------TAACTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD197.127A08 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAACTATGGCATGCACTGGGTCCGCCAGGCTCCTGGC
RhD299.127A12 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAACTTTGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD207.127A11 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCCGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD245.164E06 Vheavy      (1) GAGGTGCAGCTGGTGCAATCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCCGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD307.230E11 Vheavy      (1) CAGGTGCAGCTGGTGGAGACTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD193.126G05 Vheavy      (1) CAGGTGCAGCTGGTGGAGACCGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD296.126A03 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGAAGCGTCTGGATTCACCTTCAG------TAATTATGGCATGCACTGGTTCCGCCAGGCTCCAGGC
RhD239.126F09 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGACGTCCCTGAGATTGTCCTGTGCAGCGTCTGGGTTCACCTTTAG------AACCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD297.126E06 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------GACCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD189.181E07 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD243.109A05 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TACCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD293.109A09 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGAAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAA------TACCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD304.164B06 Vheavy      (1) CAGGTGCAGCTGGTGCAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD202.158E07 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCGGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD300.134H09 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD196.126H11 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD298.126E10 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD198.127F10 Vheavy      (1) CAGGTGCAGCTGGTGCAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAAGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TACCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD199.164E03 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD301.160A04 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD200.164G10 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGAGGAGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGGCTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD201.164H12 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAG------TAGCTATGCTATGCACTGGGTCCGCCAGGCTCCAGGC
RhD306.223E11 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD319.187A11 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TACCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD203.179F07 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAACTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD242.181A03 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAACCATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD208.179B11 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAG------GACTTCTGCCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD246.179B10 Vheavy      (1) GAGGTGCAGCTGGTGGAGACCGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD292.109A02 Vheavy      (1) CAGGTGCAGCTGGTGGAGACCGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD305.181E06 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD204.128A03 Vheavy      (1) GAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGCTTCAG------TAACTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD294.119E10 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCTCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGCTTCAG------TAACTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD303.160B11 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTGCAGCCTGAGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAG------TTCCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD206.160C06 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGTTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD302.160B10 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
RhD323.229B07 Vheavy      (1) CAGGTGCAGCTGGTGGAGTCTGGGGGA---GGCGTGGTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAG------TAGCTATGGCATGCACTGGGTCCGCCAGGCTCCAGGC
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Fig. 3B


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                                                 CDR2
                              136         --------------------------------------------------                                                  270
RhD157.119D11 Vheavy  (127) AAGGGGCTGGAGTGGGTTTCATACATTAATAGTAGGGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGAGAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGA
RhD295.119B11 Vheavy  (127) AAGGGGCTGGAGTGGATTTCATATATTAATAGTAGGGGAACACCAGATACTATGTAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCATTGTATCTGCAAATGAACAGCCTGCGA
RhD191.119E08 Vheavy  (127) AAGGGGCTGGAGTGGGTTTCATACATTAATAGTAGAGGTAATACCAAATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAAGTCACTGTACCTGCAAATGAGCAGCCTGAGA
RhD159.119B09 Vheavy  (127) AAGGGGCTGGAGTGGGTGTCATACATCAGTGGCAGAGGTAGTACAACATATTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGTCTGAGA
RhD162.119G12 Vheavy  (127) AAGGGGCTGGAGTGGGTCTCATCCATTACTAGCACTACTA------CATACTACGCAGACTCAGTGAAGGGCCGATTCAGCATCTCCAGAGACAACGCCAAGAGCACACTGTACCTGCGAATGAACAGCCTGAGA
RhD205.160B12 Vheavy  (127) AAGGGGCTGGAGTGGGTCTCATCCATTGGTAGTAGTAGTACTTACACATACTCCGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGA
RhD321.187G08 Vheavy  (127) AAGGGGCTGGAGTGGGTCTCATCCATTGGTAGTAGTAGTATTTACACATACTCCGCAGACTCAGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCACTGTATCTGCAAATGAACAGCCTGAGA
RhD192.119G06 Vheavy  (127) AAGGGACTGGAGTGGGTCTCATCCATTAGCGGTACTAGTAGTTACATATACTATGCAGACTCAGTGAAGGGCCGATTTACCATTTTCAGAGACAACGCCAAGAGCTCAGTTTATCTGCAAATGAACAGCCTGAGA
RhD163.119A02 Vheavy  (127) AAGGGACTGGAGTGGATTGGGTATATCTATTACAGTGGGAGCACCAACTACAACCC---CTCCCTCAAGAGTCGAGTCACCATAGCATTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGGTCTGTGACC
RhD241.119B05 Vheavy  (127) AAGGGACTGGAGTGGATTGGGTATATCTATTACAGTGGGAACACCAACTACAACCC---CTCCCTCAAGAGTCGAGTCACCATATCATTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGATCTGTGACC
RhD195.127A07 Vheavy  (133) AAGGGACCGGAGTGGATTGGGCGTATCTATACCAGTGGGAGTACCAACTACAACCC---CTCCCTCAAGAGTCGACTCACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGACCTCTGTGACC
RhD240.125A09 Vheavy  (130) AAGGGGCTGGAATGGATTGGGGAAATCCATCATGGTGGGAGCACCAACTACAACCC---GTCCCTCCAGAGTCGAGTCACGATATCAGTAGACAAGTCCAAGAACCGGTTCTCCCTGAAGCTGAGCTCTGTGACC
RhD317.144A02 Vheavy  (130) AAGGGGCTGGAGTGGATTGGGGAAATCCATCATGGTGGGAGCACCAACTACAACCC---GTCCCTCAAGAGTCGAGTCACGATATCAGTAGACAAGTCCAAGAACCGGTTCTCCCTGAAGCTGAGCTCTGTGACC
RhD194.126G10 Vheavy  (133) AAGGCCCTGGAGTGGCTTGCACACATTTTTTCGAATGACG--AA-AAATCCTACAGCACATCTCTGAAGAGCAGGCTCACCATCTCCAAGGACACCTCCAAAAGCCAGGTGGTCCTTACCATGACCAACATGGAC
RhD324.231F07 Vheavy  (127) AAGGGGCTGGTGTGGGTCTCACGTATTAATGTTGATGGGAAGAGCACAAGCTACGCGGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACACGCTGTACCTGCAAATGAACAGTCTGAGA
RhD244.158B10 Vheavy  (127) AAGGGACTGGAGTGGGTGGCAATTATTTGGTATGATGGGAGTAACAAACTCTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAGGAATACGTTGTATCTGCAAATGAGCAGTGTGAGA
RhD158.119B06 Vheavy  (127) AAGGGGCTCGAATGGGTGGCAGTTATTTGGTATGATGGAAGCAACAGATTCTATGCAGATTCCGTGAAGGGCCGATTCACCATCTCCAGAGATAGTTCGAAGAACATGCTGTTTCTGCAAATGGACAGCCTGAGA
RhD160.119C07 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCGGTTATATGGTATGATGGAAGTAATAGATTCTATGCGGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGCAAATGAACAACCTGAGA
RhD161.119E09 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCATTTATTTGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAATACGCTGTATCTGCAAATGAACAACCTGAGA
RhD190.119F05 Vheavy  (127) AAGGGGTTGGAGTGGGTGGCAGTTATTTGGTTTGATGGAAGTATTAAATATTATGTAGACTCCGTGAAAGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACACTGTATCTGCAAATGGACGGCCTGAGA
RhD197.127A08 Vheavy  (127) AAGGGGCTGGAATGGGTGGCAGTTATCTGGTTTGATGGAAGTAATAGAGACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACACTCTATCTGCAAATGAACAGCCTGAGA
RhD299.127A12 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAAGACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAAGACGCTCTATCTGCAAATGAACAGCCTGAGA
RhD207.127A11 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAAGACTATGTAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAGGACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD245.164E06 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCATTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGTCTGAGA
RhD307.230E11 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGGTATATGGTATGATGGAAGTAATAAATACTATGGAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD193.126G05 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAAGACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAGGAATACGCTGTATCTGCATATGAACAGCCTCAGA
RhD296.126A03 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAATTATATGGTATGATGGAAGTAATAAACACTATGCAGACCCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTCAGA
RhD239.126F09 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCATATATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCGAAGAACACGCTGTATCTGCAAATGAACAGCCTCAGA
RhD297.126E06 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAAGACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAGCACGCTGAATCTGCAAATGAACAGCCTCAGA
RhD189.181E07 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGCATCTGCAAATGAACAGCCTGAGA
RhD243.109A05 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTCAGAAATACTATGTAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD293.109A09 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD304.164B06 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD202.158E07 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTTCGATGGAAGTAATAGATACTATGGAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD300.134H09 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGAGTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCGAATGAACAGCCTGAGA
RhD196.126H11 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAAGACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD298.126E10 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATATTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAACTCCAAGAACACGCTGTATCTGCAAATGAACAGCGTGAGA
RhD198.127F10 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACACTATATCTGCAAATGAACAGCGTGAGA
RhD199.164E03 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGACGGAAGTAATAAGTACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACACTTCCAAGAACACGCTGTATCTGCAAATGAACAGCGTGAGA
RhD301.160A04 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTTTGATGGAGGTAATAAATACTATGCAGACTCCGCGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGCATCTGCAAATGAACAGCCTGAGA
RhD200.164G10 Vheavy  (130) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD201.164H12 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGCAATAAATACTACGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD306.223E11 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD319.187A11 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAAAACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACACCCTGAGA
RhD203.179F07 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD242.181A03 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD208.179B11 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGG
RhD246.179B10 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD292.109A02 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTCTGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD305.181E06 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGGTATATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAGGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD204.128A03 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTGAGAAGTACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAGGAACACGATGTATCTGCAAATGAACAGCCTGAGA
RhD294.119E10 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTGAGAAGTACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAAGGCGCTGTATCTGCAAATGAACAGCCTGAGA
RhD303.160B11 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAAAACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD206.160C06 Vheavy  (127) AAGGGGCTGGAATGGGTGGCAATTATATGGTTTGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
RhD302.160B10 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCGTTTATATCATATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTCTCTGCAAATAAACAGCCTGAGA
RhD323.229B07 Vheavy  (127) AAGGGGCTGGAGTGGGTGGCAGTTATATGGTATGATGGAAGTAATAAATATTATGCAGACTCCGTGAAGGGCCGATTCACCATCTCCCGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAGA
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Fig. 3C


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                                                                                                    CDR3
                               271                                      -----------------------------------------------------------------------                                 405
RhD157.119D11 Vheavy   (262) GCCGAGGACACGGCTGTTTATTACTGTGCGAGAGATTTGTACG-----GTGACTATGACC-----CTAAGTCCTACTAT---TACTACGGTA--TGGGCGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD295.119B11 Vheavy   (262) GCCGAGGACACGGCTGTTTACTACTGTGCGAGAGATTTGTACG-----GTGACTACGATC-----CTAAGTCCTACTAT---TACTACGGTA--TGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTCGAGT
RhD191.119E08 Vheavy   (262) GCCGAGGACACGGCTGTTTATTACTGTGCGAGAAATTTGTTCG-----GTGACTACGATC-----TTAAGTCCTACTAC---TATAACGCTA--TGGACGTCTGGGGCCAAGGCACCCTGGTCACCGTCTCGAGT
RhD159.119B09 Vheavy   (262) GCCGAGGACACGGCTGTTTATTACTGTGCGAGAGATTTGTACG-----GTGACTACGATC-----CTAAGTCCTACTAT---TACTACGCTA--TGGACGTCTGGGGCCACGGGACCACGGTCACCGTCTCGAGT
RhD162.119G12 Vheavy   (256) GCCGAGGACACGGCTGTATATTATTGTGTGAGAG-AAATCGCC-----TTTAGGGGGAGCA----CTTATTCTCGGTGG---TCGTACTACT--TTGACTTCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD205.160B12 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGAGCCTC-----TAAACTATGATTA----CATTTGGGGAGGGTA--TCGTTTCACT--AT--CCACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD321.187G08 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGAGAGCCTC-----TAAACTATGATTA----CATTTGGGGAAGGTC--TCGTCTCACT--AT--CCACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD192.119G06 Vheavy   (262) GTCGAGGACACGGCTGTCTATTACTGCGCGAGAG-ATAGATGG-----TGGGGCATGGTT-----CGGAGAGTTTTTCCC--ACCTATCCCT--TTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD163.119A02 Vheavy   (259) GCTGCGGACACGGCCGTGTATTTCTGTACGAGAGACTGGAGGCAATATGGGTCGGCGATCCGAGGTTCTCGATA-------CTACTACGGGA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD241.119B05 Vheavy   (259) GCTGCGGACACGGCCGTGTATTACTGTGCGAGAGAGTGGAGGCAGTATGGCTCGGGGATCCGAGGTTCTCGATA-------CTACTACGGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD195.127A07 Vheavy   (265) GCCGCAGACACGGCCGTGTATTACTGTGCGAGGGCC------CCTTCTTACTATGATAGTAGTGGTTATCGTTA-------CTGGTAC---A--TCGATCTCTGGGGCCGTGGCACCCTGGTCACCGTCTCGAGT
RhD240.125A09 Vheavy   (262) GCCGCGGACACGGCCGTATATCACTGTGCGAGGGGG------AGGAGTTATTATGATAGTAGTGGGCATTCCTTTCGCGGTCTGGTACC-TT--TTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCGAGT
RhD317.144A02 Vheavy   (262) GCCGCGGACACGGCCGTGTATTACTGTGCGAGGGGG------ACGTCTTATTATGATAGTAGTGGTTATTCCTTTCGCGGTCTGGTAGC-TT--TTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCGAGT
RhD194.126G10 Vheavy   (265) CCTGTGGACACAGCCACATATTACTGTGCACG-GATGAGGCTTACTATGGTTCGGGGAGTT---------ATTACGTACTACTACTACAGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD324.231F07 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCAAGAGATCCCCGAC-----GATTTTTGGAGTGGGC--------------CCGCTA---CGGTA--TGGACGTCTGGGGCCGAGGGACCACGGTCACCGTCTCGAGT
RhD244.158B10 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGA-CTCT---------GTTCGGGGAGTCAGTAGATGGGGACTCAGAAATATTACGCTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD158.119B06 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAAATTTCC-------ATGAAAGTAGT------GATCCGCAGACAC------TACGTTA--TGGACGTCTGGGGCCACGGGACCACGGTCACCGTCTCGAGT
RhD160.119C07 Vheavy   (262) GCCGAGGACACGGCTCTCTATTCCTGTGCGAGAGAGATTACT-------ACGACAGTAGT------GGTCCGAAGACAC------TACCTTA--TGGACATCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD161.119E09 Vheavy   (262) GCCGAGGACTCGGCTGTGTATTACTGTGCGAGAGA----G---------GAAATAGCAGCTCGTCTTTATTCTCGCTACCACT---ACGCTA--TGGACGTCTGGGGCCAAGGGACAATGGTCACCGTCTCGAGT
RhD190.119F05 Vheavy   (262) GCCGAGGAGACGGCTATATATTTCTGTGCGAGAGAAA----A---TAGTGTTCTAGTCCCA-GGT-----A--CTATACGGAGGCGATATTATTTGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD197.127A08 Vheavy   (262) GCCGAGGACACGGCTGTTTATTACTGTGCGACAGA--------------GTT---GGCC-----------------AGAGGGCGGCTACGAGCCCTAGAGTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD299.127A12 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGA--------------GTT---GGCC-----------------AGAGGGCGGCTACGAGACCTAGACTACTGGGGCCAGGGCACCCTGGTCACCGTCTCGAGT
RhD207.127A11 Vheavy   (262) GCCGAGGACACAGCTGTGTATTACTGTGCGAGAGA--------------GTT---GGCC-----------------AAAGGGCGGCTACGAGACCTAGACCACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD245.164E06 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCTCCGGAACCACGTTTTTGGAGTG-GTT-----A--TTCTACCTCT----------TTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD307.230E11 Vheavy   (262) GCCGACGACACGGCTGTGTATTACTGTGCGAGGGAAC------ACGGCGGGTCTAGGAGTG-GCTGGTACA--CTTTACGTCTCGCGTACTACTTTGACTACTGGGGCCAGGGCACCCTGGTCACCGTCTCGAGT
RhD193.126G05 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGATCGCCTCCCGTGGATATAGTCG-----------------CTACTTAT---AC--TACTTTGACTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD296.126A03 Vheavy   (262) GCCGAGGACACGGCTGTGTATTTCTGTGCGAGAGAGATCGCCTCCCGTGGATATAGTCG-----------------CTACTTAT---AC--TACTTTGACTCCTGGGGCCAGGGAACCCTGGTCACCGTCTCGAGT
RhD239.126F09 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGATCGCCTCCCGTGGATATAGTCG-----------------CTACTTAT---AC--TACTTTGACTCCTGGGGCCAGGGCACCCTGGTCACCGTCTCGAGT
RhD297.126E06 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGATCGCCTCCCGTGGATATAGTCG-----------------GTACTTAT---AC--TACCTTGACTTCTGGGGCCAGGGCACCCTGGTCACCGTCTCGAGT
RhD189.181E07 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACATGGTTACT-ATGGTTCGGGGAGCC-TACAGA-A-ACTACTA---CTACTACGGTA--TGGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCGAGT
RhD243.109A05 Vheavy   (262) GCCGAGGACACGGCTGTCTATTACTGTGCGAGAGA---GGTTGC----GGTTCGGGGAGTT-ATTCG--------CTA---CTACTACGGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD293.109A09 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGA---GGTTGC----GGTTCGGGGAGTT-ATTCG--------CTA---CTACTACGCTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD304.164B06 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGACAGTGGT----GGTAGCTGCCAAA-ATACGA-A-ACCACTA---CTACTACGCTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD202.158E07 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGTTCT----ATACACGTAGCGGGCTA-TGGTCACAA--GGGTACTCCT---AT--TACATGGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCGAGT
RhD300.134H09 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGTTCT----ATACACGTAGCGGGCTA-TGGTCACAA--GGGTACTCCT---AT--TACATGGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCGAGT
RhD196.126H11 Vheavy   (262) GCCGAGGACACGGCTGTTTATTACTGTGCGAGAGAATTGAGC-------AC----GCAAC--GTGGATACAGCCGCTACCA---CTATGTTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD298.126E10 Vheavy   (262) GCCGAGGACACGGCTGTTTATTACTGTGCGAGAGATTTGAGC-------AC----GCAAC--GTGGATACAGCCGCTACTA---CTATGTTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD198.127F10 Vheavy   (262) GTCGAGGACACGGCTGTTTATTACTGTGCGAGAGATTTGACC-------AC----GCAAC--GTGGATACAGCCGCTATCA---CTATGTTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD199.164E03 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGA---AGTG------GGTTTTGGCAGTG-GCTGGT-C--ACGATA---CTACTACGGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD301.160A04 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGA---TGCGTCG-GTGCTTTCTGGATTG-GTTACT-CGAAGGTTAGT-CTACTACGGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD200.164G10 Vheavy   (265) GCTGAGGACACGGCTGTGTATTACTGTGCGAGAGAGAGTACTC------TGTATAGCAGCA-GCTGGTACAGGAGGTACTACTACTACGGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD201.164H12 Vheavy   (262) GCTGAGGACACGGCTGTGTATTACTGTGCGAGAGAGAGTACTC------TATATAGCAGCA-GCTGGTACAGGAGGTACTACTACTACAGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD306.223E11 Vheavy   (262) GACGACGACACGGCTGTGTATTACTGTGCGAGAGAGGGTACTC------TGTATAGCAGCA-GCTGGTACAGGAGGTACTACTACTACGGTA--TGGACGCCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD319.187A11 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGACCTACAAG------GGTATAGAAGCA-GCTGGTACCGGATGTACTACTACTACGGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD203.179F07 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGATGGTCT------CCTATAGCAGCA-GCTGGTACCGCCGCTACTACTACTACGTTA--TGGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCGAGT
RhD242.181A03 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGATGGCCT------CCTATAGCAGCA-GCTGGTACCGCCGCTACTACTACTACGTTA--TGGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCGAGT
RhD208.179B11 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGATGGTCT------CCTATAGCAGCA-GCTGGTACCGCCGCTACTACTACTACAATA--TGGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCGAGT
RhD246.179B10 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGATGGTCT------CCTATAGCAGCA-GCTGGTACCGCCGCTACTACTACTACAATA--TGGACGTCTGGGGCAAAGGGACCACGGTCACCGTCTCGAGT
RhD292.109A02 Vheavy   (262) GCCGAGGACACGGCTGTGTTTTACTGTGCGAGAGAGCAAGGGG------GGTATAGCAGCA-GTTGGTACCGCCGCTACTACTACTACTATA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD305.181E06 Vheavy   (262) GCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAGCAAGGGG------GGTATAGCAGCA-GTTGGTACCGCCGCTACTACTACTACAATA--TGGACCTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD204.128A03 Vheavy   (262) GCTGAGGACACGGCTATGTATTATTGTAAGAA---TAAAGTGG------GAGCTACCCG---GCGGG--CAGTCGTT-----------GCTT--TTGATATCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD294.119E10 Vheavy   (262) GCTGAGGACACGGCTATGTATTATTGTAAGAA---TAAAGTGG------GAGCTACCCG---GCGGG--CAGTTGTT-----------GCTG--TTGATATTTGGGGCCAAGGGACAATGGTCACCGTCTCGAGT
RhD303.160B11 Vheavy   (262) GCTGAGGACACGGCTGTGTATTACTGTGCGAAAGATGAAGTGG------GGTATAGCAGCA-GCTGGTACAGGCGCTACTACTACTACGCTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD206.160C06 Vheavy   (262) GCTGAGGACACGGCTGTGTATTACTGTGCGAAAGAGCACGGCT------ATTATAGCAGCA-GCTGGTACCGAAACTACTATTACTACGCTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD302.160B10 Vheavy   (262) GCTGAGGACACGGCTGTGTATTACTGTGCGAAAGAGCACGGCT------ATTATCGCAGCA-GCTGGTACCGAAACTACTACTACTATGGGA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
RhD323.229B07 Vheavy   (262) GCTGAGGACACGGCTGTGTATTACTGTGCGAGAGATTGGGTCA------CTCGCAGCAGCA-ACTGGTACAGGAACTACTACTACTACGGTA--TGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCGAGT
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Fig. 4A

CDR1

CDR2

Fig. 4C

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                                            CDR3
                           281  ------------------------------------------                                                          420
RhD157.119D11 Kappa   (257) ATTACTGTCAGCAGCGTAGCAGCT---GGCCTCCGATGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD159.119B09 Kappa   (260) ATTTTTGTCAGCAATATGGAACCT---CAC---CGGGGGTCACTTTCGGCCAAGGGACACGACTGGAAATTGAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGG
RhD295.119B11 Kappa   (260) ATTACTGTCAGCACTATGGTAGCT---CAC---CTCCCATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD317.144A02 Kappa   (260) ATTACTGTCAGCAGTATGGCAGCT---------TTTCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD305.181E06 Kappa   (260) ATTACTGTCAGCATTTTGGTAACT---CAC---GG---GGAACGTTCGGCCAAGGGACCAAGGTGGAAATCAGACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD163.119A02 Kappa   (260) ATTACTGTCAGGTCTATGGTAGCT---CAC---CTCTGTACACTTTTGGCCAGGGGACCAAGGTGGAGATGAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD191.119E08 Kappa   (260) ATTATTGTCAGCACTATGATGACT---CAATTTCGACGTACATTTTTGGCCCGGGGACCGAGCTGGAGATCAAGCGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD294.119E10 Kappa   (260) ATTTCTGTCAGCTGTATGATCACT---CACGTCCGATGTACACTTTTGGCCAGGGGACTAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD202.158E07 Kappa   (260) ATTACTGTCAGCAGTATGGTACTG---CAC---CC---TACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD241.119B05 Kappa   (260) ATTACTGTCAGCAGTATGGTAGCT---CAC---CTCTATACTCTTTTGGCCAGGGGACCAAGGTGGACATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD242.181A03 Kappa   (260) ATTACTGTCAGCAGTATGGTAGCT---CAC---GG---TACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD306.223E11 Kappa   (260) ATTACTGTCACTATTCTGGTGGCT---CAC---CTCCGTACCCTTTTGGCCAGGGGACCAGGCTGGACATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD189.181E07 Kappa   (257) ATTACTGTCAGCAGTATAATAACT---GGCCGACCCTGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD324.231F07 Kappa   (257) ATTACTGTCAGCAGTATAATAACT---GGC---CCCGGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD201.164H12 Kappa   (257) ATTACTGTCAGCAGTATAATAACT---GGCCTCCCATATTCACTTTCGGCCCTGGGACCAAACTGGATATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD303.160B11 Kappa   (260) ATTACTGTCAACACTATCATGACT---GGCCTCCG------ACCTTCGGCCAAGGGACACGACTGGAGATTAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD301.160A04 Kappa   (272) ATTACTGCATGCAAGGTCTACGAA---CTC------CGTACACTTTCGGCCAGGGGACCAAGCTGGAGATCAAGCGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD304.164B06 Kappa   (257) ACTTCTGTCAGCACTCTTACAGAA---G------TGGGCGGGCGTTCGGCCAAGGGACCACGGTGGAGGTGAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD158.119B06 Kappa   (257) ATTACTGTCACACGTATAACAGTG---C------CCCCTTCGCTTTCGGCCCTGGGACCAAAGTGGATATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD160.119C07 Kappa   (257) ATTACTGTCAAAAGTATAACAGTG---C------CCCCTTCGCTTTCGGCCCTGGGACCAAAGTGGATATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD162.119G12 Kappa   (257) ACTACTGTCTACAGGCTAACAGGT---T------CCCCCTCTCTTTCGGCGGAGGGACCAGGGTAGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD192.119G06 Kappa   (257) ACTATTGTCAACAGGCTAACAGTT---T------CCCTCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD161.119E09 Kappa   (257) ATTACTGTCAACAGCTTAGTAGTT---ACC---CTCCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD240.125A09 Kappa   (257) ATTACTGCCAACAGTATAATAGTT---T------TCCGTACACCTTTGGCCAGGGGACCAAGCTGGAGTTCACACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD205.160B12 Kappa   (257) ATTACTGTCAACAACTTAATAGTT---ATT---CCAGGTGGGCGTTCGGCCAAGGGACCAAGGTGGAAGTCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD190.119F05 Kappa   (257) TCTACTGTCAACAGACTTACAGT------C---CCCCTTACACTTTTGGCCAGGGAACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD198.127F10 Kappa   (257) ACTACTGTCAACAGAGTTACAGTA---CCC---CCCCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD298.126E10 Kappa   (257) ACTACTGTCAACAGAGTTACAGTA---CCC---CCCCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAGCGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD239.126F09 Kappa   (257) ACTACTGTCAACAGAGTTACAGTA---CCC---CCCCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD292.109A02 Kappa   (257) ACTACTGTCAACAGAGTTACAGTA---GTT---CTGTGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD195.127A07 Kappa   (257) ACTACTGTCAACAGAGTTACAGT----AGA---G---G--GACGTTCGGCCAAGGGACTAAGGTGGAAATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD307.230E11 Kappa   (257) ACTACTGTCTCCAGAGTTTCACTG---TCC---CT---CGGACTTTCGGCCCTGGGACCAAAGTGGATGTCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD193.126G05 Kappa   (257) ACTACTGTCAACAGAGTTACAGTA---CCC---TCGCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD297.126E06 Kappa   (257) ACTACTGTCAACAGAGTTACAGTA---CCC---TCGCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD296.126A03 Kappa   (257) ACTACTGTCAACAGAGTTACAGTT---CCC---TCGCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD206.160C06 Kappa   (257) ACTACTGTCAACAGAGTTACCGTA---CCC---AAGGTCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD245.164E06 Kappa   (257) ACTACTGTCAACATAGTTACAGTA---CCC---CTG---TCACGTTCGGCCAAGGGACCAAGGTGGAAGTCAAGCGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD243.109A05 Kappa   (257) ACAACTGTCAACAGAGTTACAGTG---ACC---C---GTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD244.158B10 Kappa   (257) ACTACTGCCAACAGAGTTACAGA----ACT---C---G--GACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD199.164E03 Kappa   (257) ACTACTGTCAACAGAGTTACAGTA---CCT---CCACGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD200.164G10 Kappa   (257) ACTACTGTCAACAGAGTTACAGTA---CCT---C---GTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD293.109A09 Kappa   (257) ACTACTGTCAACAGAGTTACACTA---CCC---TC---TGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD194.126G10 Kappa   (257) ACTACTGTCAACAGACTTACAGAA---CCC---CCACGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD196.126H11 Kappa   (257) ACTACTGTCAACAGAGTTACGGAA---CCC---CCACGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAGCGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD302.160B10 Kappa   (257) ACTACTGTCAACAGACTTACAGTA---CCC---TT---TGGACGTTCGGCCAAGGGACCAAGGTGGAAATCACACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD323.229B07 Kappa   (257) ACTACTGTCAACAGTATTACAGAA---CGC---CCACGTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGAA---CTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGA
RhD197.127A08 Lambda  (263) ATTACTGCCTGCTCTTCTATGGT---GGTGCTCAGCTGGGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
RhD299.127A12 Lambda  (263) ATTACTGCCTGCTCTTCTATGGT---GGTGCTCAGCTGGGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
RhD207.127A11 Lambda  (263) ATTACTGCCTGCTCTTCTATGGT---GGTGCTCAACTGGGGGTGTTCGGCGGAGGGACCAAACTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
RhD319.187A11 Lambda  (263) ATTACTGCCTGCTCTACTATGGT---GGTGCTCAGCGTTGGGTGTTCGGCGGAGGGACCATCCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
RhD208.179B11 Lambda  (263) ATTACTGCCTGCTCTACTATGGT---GTTCCTCAGCCAGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
RhD300.134H09 Lambda  (263) ATTACTGTGTGCTGTA-TATGG-----GTAGTGGCCCTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCACCCTCCTCTGAGGAGCTTCAAGCCAAC
RhD203.179F07 Lambda  (263) ATTCCTGCTGCTCATATG----CAG--GCACCTACAGTTATGTCTTCGGAACTGGGACCAAGGTCACCGTCCTGAGTCAGCCCAAGGCCAACCCCACTGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTCCAAGCCAAC
RhD204.128A03 Lambda  (257) ATTACTGTAACTCCCGGGACAGCAGTGGTAATTATCGGGAGCTATTCGGCGGAGGGACCAAGCTGACCGTCCTTGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
RhD246.179B10 Lambda  (257) ATTACTGTAACTCCCGGGACACCA---GTACTGACCATTATGTCTTCGGAGATGGGACCAGGGTCACCGTCGTAGGTCAGCCCAAGGCCAACCCCACTGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTCCAAGCCAAC
RhD321.187G08 Lambda  (269) ACTACTGTCAGTCTTATGA---------TAGTAACAATTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCCTCTGAGGAGCTTCAAGCCAAC
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Fig. 4D


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                              421                                                                                                                                        560
RhD157.119D11 Kappa   (391) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
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RhD295.119B11 Kappa   (391) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGGGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD317.144A02 Kappa   (388) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD305.181E06 Kappa   (388) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD163.119A02 Kappa   (391) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD191.119E08 Kappa   (394) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD294.119E10 Kappa   (394) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD202.158E07 Kappa   (388) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD241.119B05 Kappa   (391) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
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RhD306.223E11 Kappa   (391) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD189.181E07 Kappa   (391) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD324.231F07 Kappa   (388) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD201.164H12 Kappa   (391) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
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RhD301.160A04 Kappa   (400) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
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RhD206.160C06 Kappa   (388) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD245.164E06 Kappa   (385) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
RhD243.109A05 Kappa   (385) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
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RhD302.160B10 Kappa   (385) ACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGATAAC-GCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCC
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RhD319.187A11 Lambda  (400) AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT----GGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGG
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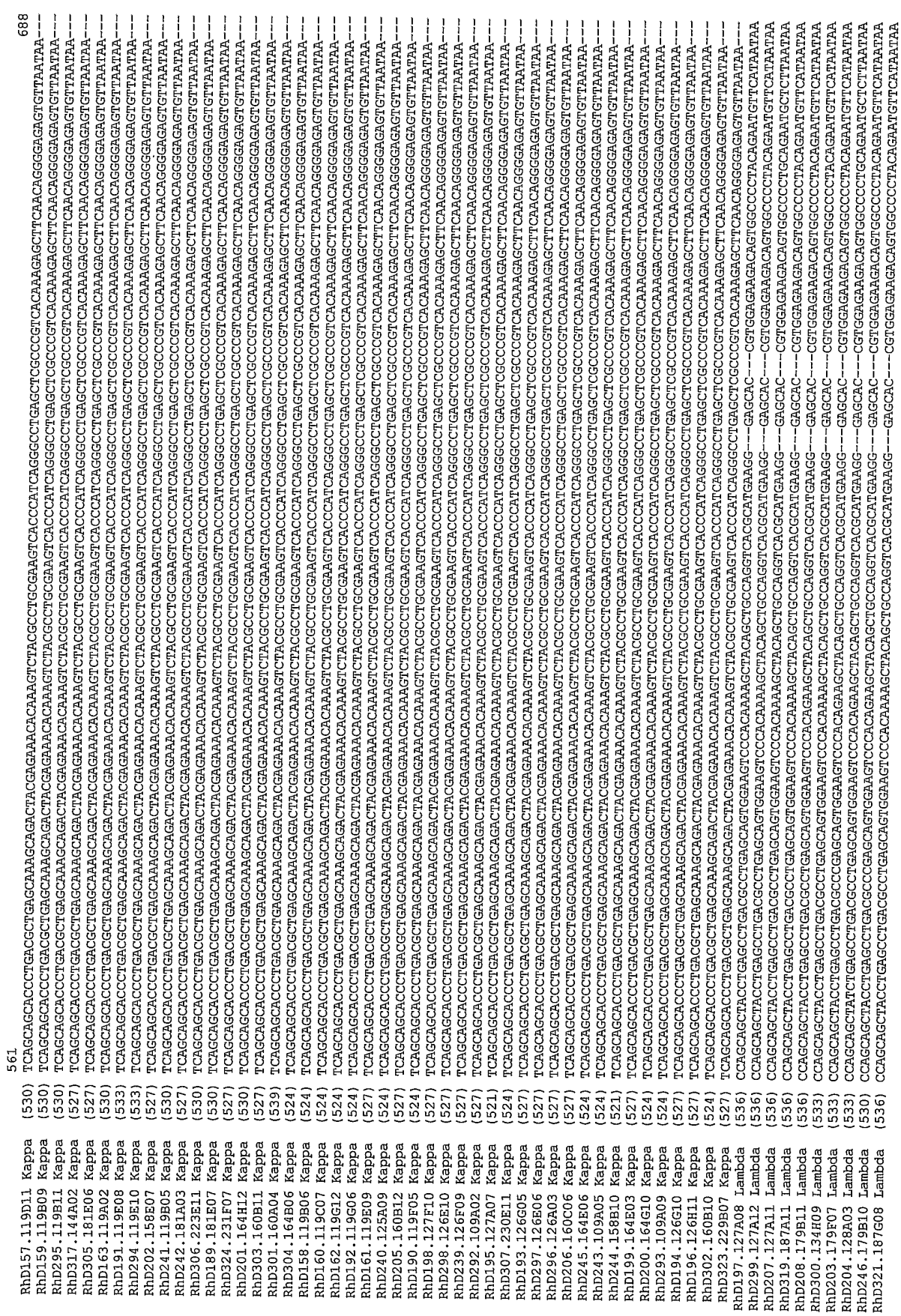
RhD321.187G08 Lambda  (400) AAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGT----GGAGACCACCACACCCTCCAAACAAAGCAACAACAAGTACGCGG
```

Fig. 4E


561
688
RhD157.119D11 Kappa (530) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD159.119B09 Kappa (530) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
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RhD317.144A02 Kappa (527) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD305.181E06 Kappa (527) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
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RhD191.119E08 Kappa (533) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
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RhD201.164H12 Kappa (530) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
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RhD244.158B10 Kappa (521) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD199.164E03 Kappa (527) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD200.164G10 Kappa (524) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD293.109A09 Kappa (524) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD194.126G10 Kappa (527) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD196.126H11 Kappa (527) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD302.160B10 Kappa (524) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD323.229B07 Kappa (527) TCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAATAA---
RhD197.127A08 Lambda (536) CCAGCAGCTACCTGAGCCTGAGCCCTGAGCAGTGGAAGTCCCACAAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAATAA
RhD299.127A12 Lambda (536) CCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAATAA
RhD207.127A11 Lambda (536) CCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAATAA
RhD319.187A11 Lambda (536) CCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTGCAGAATGTTCATAATAA
RhD208.179B11 Lambda (536) CCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAATAA
RhD300.134H09 Lambda (533) CCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAATAA
RhD203.179F07 Lambda (533) CCAGCAGCTACCTGAGCCTGACGCCCGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAATAA
RhD204.128A03 Lambda (533) CCAGCAGCTATCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTGCAGAATGTTCATAATAA
RhD246.179B10 Lambda (530) CCAGCAGCTACCTGAGCCCGAGCAGTGGAAGTCCCACAGAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAATAA
RhD321.187G08 Lambda (536) CCAGCAGCTACCTGAGCCTGACGCCTGAGCAGTGGAAGTCCCACAAAGCTACAGCTGCCAGGTCACGCATGAAGG---GAGCAC---CGTGGAGAAGACAGTGGCCCCTACAGAATGTTCATAATAA

Fig. 5

		FR1			CDR1	FR2	CDR2	FR3	CDR3
		1 2 3				4	5 6	7 8 9	10 11 12
		1234567890	12345678901234567890		1ab2345	67890123456789	012a3456789012345	67890123456789012abc345678901234*	*5678901234567890123456789012345*
RhD157.119D11	Vheavy	(1)	EVQLVESGGG-LVQPGGSLRLSCVASGFTFR		S--FDMN	WVRQAPGKGLEWVS	YINSRGSTIYYADSVKG	RFTISRENAKNSLYLQMNSLRAEDTAVYYCAR	DL--YGDYDPKSYYYYGMGVWGQGTTVTVSS
RhD158.119B06	Vheavy	(1)	EVQLVETGGG-VVQPGRSLRLSCAASGFSFS		N--FGFH	WIRQSPGKGLEWVA	VIWYDGSNRFYADSVKG	RFTISRDSSKNMLFLQMDSLRAEDTAVYYCAR	----EISMKVVIRRHYVMDVWGHGTTVTVSS
RhD159.119B09	Vheavy	(1)	EVQLVETGGG-LVQPGGSLRLSCAASGFSFR		S--YDMN	WVRQAPGKGLEWVS	YISGRGSTTYYADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	DL--YGDYDPKSYYYYAMDVWGHGTTVTVSS
RhD160.119C07	Vheavy	(1)	EVQLVESGGG-VVQPGRSLRLSCAASGFTFS		N--YGMH	WVRQAPGKGLEWVA	VIWYDGSNRFYADSVKG	RFTISRDNSKNTLYLQMNNLRAEDTALYSCAR	----EITTTVVVRRHYLMDIWGQGTTVTVSS
RhD161.119E09	Vheavy	(1)	EVQLVESGGG-VVQSGRSLRLSCAASGFTFS		N--NGMH	WVRQAPGKGLEWVA	FIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMDGLRAEDSAVYYCAR	E---EIAARLYSRYHYAMDVWGQGTMVTVSS
RhD162.119G12	Vheavy	(1)	QVQLVESGGG-LVKPGGSLRLSCAASGFGFS		A--YSMN	WVRQAPGKGLEWVS	SIT--STTTYYADSVKG	RFSISRDNAKSTLYLRMNSLRAEDTAVYYCVR	EI--AFRGSTYSRWSYYFDFWGQGTLVTVSS
RhD163.119A02	Vheavy	(1)	QVQLQESGPG-LVKPSETLSLTCTVSGGSIS		S--YYWS	WVRQPPGKGLEWIG	YIYY-SGSTNYNPSLKS	RVTIALDTSKNQFSLKLRSVTAADTAVYFCTR	DWRQYGSAIRGSRYYYGMDVWGQGTTVTVSS
RhD189.181E07	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DMVTMVRGAYRNYYYYGMDVWGKGTTVTVSS
RhD190.119F05	Vheavy	(1)	EVQLVETGGG-VVQPGRSLRLSCAASGFSFS		N--YGMH	WVRQAPGKGLEWVA	VIWFDGSIKYYVDSVKG	RFTISRDNSKNTLYLQMNSLRAEETAIYFCAR	EN--SVLVPGTIRRYYLDYWGQGTLVTVSS
RhD191.119E08	Vheavy	(1)	QVQLVESGGD-LVQPGGSLRLSCAASGFTFR		S--YEMN	WVRQAPGKGLEWVS	YINSRGNTKYYADSVKG	RFTISRDNAKKSLYLQMSSLRAEDTAVYYCAR	NL--FGDYDLKSYYYNAMDVWGQGTLVTVSS
RhD192.119G06	Vheavy	(1)	QVQLVESGGG-LVKPGGSLRLSCAASGFTFS		S--YAMN	WVRQAPGKGLEWVS	SISGTSSYIYYADSVKG	RFTIFRDNAKSSVYLQMNSLRVEDTAVYYCAR	DR--WWGMVRRVFPTYPFDYWGQGTLVTVSS
RhD193.126G05	Vheavy	(1)	QVQLVETGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKDYADPVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EIASR----GYSRYLYYFDSWGQGTLVTVSS
RhD194.126G10	Vheavy	(1)	QVTLKESGPV-LVKPTETLTLTCTVSGFSLS		NARMGVS	WIRQPPGKALEWLA	HIF-SNDEKSYSTSLKS	RLTISKDTSKSQVVLTMTNMDPVDTATYYCAR	MRLTMVRGVITY-YYYSMDVWGQGTTVTVSS
RhD195.127A07	Vheavy	(1)	QVQLQESGPG-LVKPSQTLSLTCTVSGGSIS		SGSYYWS	WIRQPAGKGPEWIG	RIY-TSGSTNYNPSLKS	RLTISVDTSKNQFSLKLTSVTAADTAVYYCAR	APSYYDSSGYRY---WYIDLWGRGTLVTVSS
RhD196.126H11	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKDYADSVKG	RFTISRDNSKNTLYLQMNSVRAEDTAVYYCAR	ELSTQR---GYSRYHYVMDVWGQGTTVTVSS
RhD197.127A08	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		N--YGMH	WVRQAPGKGLEWVA	VIWFDGSNRDYADSVKG	RFTISRDNSKKTLYLQMNSLRAEDTAVYYCAT	ELAR---------GRLRALEYWGQGTLVTVSS
RhD198.127F10	Vheavy	(1)	QVQLVQSGGG-VVQPGKSLRLSCAASGFTFS		T--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDTSKNTLYLQMNSVRVEDTAVYYCAR	DLTTQR---GYSRYHYVMDVWGQGTTVTVSS
RhD199.164E03	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLHLQMNSLRAEDTAVYYCAR	-EVGFGSGWSR--YYYGMDVWGQGTTVTVSS
RhD200.164G10	Vheavy	(1)	EVQLVESGGGGVVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	ESTLYSSSWYRRYYYYGMDVWGQGTTVTVSS
RhD201.164H12	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YAMH	WVRQAPGKGLEWVA	VISYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	ESTLYSSSWYRRYYYYSMDVWGQGTTVTVSS
RhD202.158E07	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWFDGSNRYYGDSVKG	RVTISRDNSKNTLYLRMNSLRAEDTAVYYCAR	EFYTRSGLWSQGYSYY-MDVWGKGTTVTVSS
RhD203.179F07	Vheavy	(1)	EVQLVESGGG-VVQPGRSLRLSCAASGFTFS		N--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EMVSYSSSWYRRYYYYVMDVWGKGTTVTVSS
RhD204.128A03	Vheavy	(1)	EVQLVESGGG-VVQPGRSLRLSCAASGFSFS		N--YGMH	WVRQAPGKGLEWVA	VISYDGSEKYYADSVKG	RFTISRDNSKKALYLQMNSLRAEDTAMYYCKN	------KVGATRRAVVAFDIWGQGTTVTVSS
RhD205.160B12	Vheavy	(1)	EVQLVETGGG-LVKPGGSLRLSCAASGFTFR		S--YSMN	WVRQAPGKGLEWVS	SIGSSSTYTYSADSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	GE--PLNYDYIWGGYRFTIHWGQGTLVTVSS
RhD206.160C06	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	IIWFDGSNKYYADSVKG	RFTISRDNSKNTLYLQINSLRAEDTAVYYCAK	EHGYYSSSWYRNYYYYAMDVWGQGTTVTVSS
RhD207.127A11	Vheavy	(1)	EVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKDYVDSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	ELAK---------GRLRDLDHWGQGTLVTVSS
RhD208.179B11	Vheavy	(1)	EVQLVESGGG-VVQPGRSLRLSCAASGFTFR		T--SAMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EMVSYSSSWYRRYYYYNMDVWGKGTTVTVSS
RhD239.126F09	Vheavy	(1)	QVQLVESGGG-VVQPGTSLRLSCAASGFTFR		T--YGMH	WVRQAPGKGLEWVA	YIWYDGSNKYYADSVKG	RFTISRDNSKSTLNLQMNSLRAEDTAVYYCAR	EIASR----GYSRYLYYFDSWGQGTLVTVSS
RhD240.125A09	Vheavy	(1)	QLQLQESGPG-LVKPSGTLSLTCAVSGGSMR		S-SNWWT	WVRQPPGKGLEWIG	EIH-HGGSTNYNPSLQS	RVTISVDKSKNRFSLKLSSVTAADTAVYHCAR	GRSYYDSSGHSFRGLVPFDIWGQGTMVTVSS
RhD241.119B05	Vheavy	(1)	QVQLQESGPG-LVKPSETLSLICTVSGGSIS		S--NYWS	WIRQPPGKGLEWIG	YIY-YSGNTNYNPSLKS	RVTISLDTSKNQFSLKLRSVTAADTAVYYCAR	EWRQYGSGIRGSRYYYGMDVWGQGTLVTVSS
RhD242.181A03	Vheavy	(1)	EVQLVESGGG-VVQPGRSLRLSCAASGFTFS		N--HGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EMASYSSSWYRRYYYYVMDVWGKGTTVTVSS
RhD243.109A05	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		T--YGMH	WVRQAPGKGLEWVA	VIWYDGSQKYYVDSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	-EVAVRGVIR---YYYGMDVWGQGTTVTVSS
RhD244.158B10	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFSFS		S--YGMH	WVRQAPGKGLEWVA	IIWYDGSNKLYADSVKG	RFTISRDNSRNTLYLQMSSVRAEDTAVYYCAR	DSVRGVSRWG-TQKYYAMDVWGQGTTVTVSS
RhD245.164E06	Vheavy	(1)	EVQLVQSGGG-VVQPGRSPRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	FIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DLRNH---VEWSGYSTSFDYWGQGTLVTVSS
RhD246.179B10	Vheavy	(1)	EVQLVETGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EMVSYSSSWYRRYYYYNMDVWGKGTTVTVSS
RhD292.109A02	Vheavy	(1)	QVQLVETGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWSDGSNKYYADSVKG	RFTISRDNSRNTLYLQMNSLRAEDTAVFYCAR	EQGGYSSSWYRRYYYYYMDVWGQGTTVTVSS
RhD293.109A09	Vheavy	(1)	EVQLVESGGG-VVQPGRSLRLSCAASGFTFN		T--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	-EVAVRGVIR---YYYAMDVWGQGTTVTVSS
RhD294.119E10	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFSFS		N--YGMH	WVRQAPGKGLEWVA	VISYDGSEKYYADSVKG	RFTISRDNSKKTLYLQMNSLRAEDTAMYYCKN	------KVGATRRAVVAVDIWGQGTMVTVSS
RhD295.119B11	Vheavy	(1)	QVQLVESGGG-LVQPGGSLRLSCVGSGFTFR		S--FDMN	WVRQAPGKGLEWIS	YINSRGNTRYYVDSVKG	RFTISRDNAKNSLYLQMNSLRAEDTAVYYCAR	DL--YGDYDPKSYYYYGMDVWGQGTMVTVSS
RhD296.126A03	Vheavy	(1)	EVQLVESGGG-VVQPGRSLRLSCEASGFTFS		N--YGMH	WFRQAPGKGLEWVA	IIWYDGSNKHYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVFYCAR	EIASR----GYSRYLYYFDSWGQGTLVTVSS
RhD297.126E06	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFR		T--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKDYADSVKG	RFTISRDNSKNTLHLQMNSLRAEDTAVYYCAR	EIASR----GYSRYLYYLDFWGQGTLVTVSS
RhD298.126E10	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSVRAEDTAVYYCAR	DLSTQR---GYSRYYYVMDVWGQGTTVTVSS
RhD299.127A12	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		N--FGMH	WVRQAPGKGLEWVA	VIWYDGSNKDYADSVKG	RFTISRDNSKRTLYLQMNSLRAEDTAVYYCAR	ELAR---------GRLRDLDYWGQGTLVTVSS
RhD300.134H09	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	EFYTRSGLWSQGYSYY-MDVWGKGTTVTVSS
RhD301.160A04	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWFDGGNKYYADSAKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DASVLSGLVTRRLVYYGMDVWGQGTTVTVSS
RhD302.160B10	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	FISYDGSNKYYADSVKG	RFTISRDNSKNTLSLQMNSLRAEDTAVYYCAK	EHGYYRSSWYRNYYYYGMDVWGQGTTVTVSS
RhD303.160B11	Vheavy	(1)	QVQLVESGGG-VVQPERSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VISYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	DEVGYSSSWYRRYYYYAMDVWGQGTTVTVSS
RhD304.164B06	Vheavy	(1)	QVQLVQSGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	-ETVVVAAKIRNHYYYAMDVWGQGTTVTVSS
RhD305.181E06	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	GIWYDGSNKYYADSVKG	RFTISRDNSRNTMYLQMNSLRAEDTAVYYCAR	EQGGYSSSWYRRYYYYNMDLWGQGTTVTVSS
RhD306.223E11	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNTLRDDDTAVYYCAR	EGTLYSSSWYRRYYYYGMDAWGQGTTVTVSS
RhD307.230E11	Vheavy	(1)	QVQLVETGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	GIWYDGSNKYYGDSVKG	RFTISRDNSRNTLYLHMNSLRADDTAVYYCAR	EHGGSRSGWYTLRLAYYFDYWGQGTLVTVSS
RhD317.144A02	Vheavy	(1)	QVQLQESGPG-LVKPSGTLSLTCAVSGGSIR		G-SNWWS	WVRQPPGKGLEWIG	EIH-HGGSTNYNPSLKS	RVTISVDKSKNRFSLKLSSVTAADTAVYYCAR	GTSYYDSSGYSFRGLVAFDIWGQGTMVTVSS
RhD319.187A11	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		T--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKNYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DLQGYRSSWYRMYYYYGMDVWGQGTTVTVSS
RhD321.187G08	Vheavy	(1)	EVQLVESGGG-LVKPGGSLRLSCAASGFTFR		S--YSMN	WVRQAPGKGLEWVS	SIGSSSIYTYSADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	GE--PLNYDYIWGRSRLTIHWGQGTLVTVSS
RhD323.229B07	Vheavy	(1)	QVQLVESGGG-VVQPGRSLRLSCAASGFTFS		S--YGMH	WVRQAPGKGLEWVA	VIWYDGSNKYYADSVKG	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	DWVTRSSNWYRNYYYYGMDVWGQGTTVTVSS
RhD324.231F07	Vheavy	(1)	EVQLVESGGG-LVQPGRSLRLSCVASGFTFS		S--YWMH	WVRQVPGKGLVWVS	RINVDGKSTSYADSVKG	RFTISRDNAKNTLYLQMNSLRAEDTAVYYCAR	DP-RR----FLEWARYGMDVWGRGTTVTVSS

*Numbering after amino acid 94 does not follow Clothia.

Fig. 6A

		FR1	CDR1	FR2	CDR2	FR3	CDR3
		1 2	3	4	5	6 7 8	9 * 10
		1234567890123456789012345	45678901acdef234	567890123456789	0123456	78901234567890123456789012345678	901234567890123456789
RhD157.119D11	kappa	(1) EIVLTQSPATLSLSPGERATLSC	RASQSVSS-----YLA	WYQQKRGQAPRLLIF	NASNRAT	GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC	QQRSSWPPMYTFGQGTKLEIKR
RhD189.181E07	Kappa	(1) EIVMTQSPATLSVSPGERATLSC	RASQSVSS-----NLA	WYQQKPGQAPRLLIY	GASTRAT	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNNWPTLYTFGQGTKLEIKR
RhD324.231F07	Kappa	(1) EIVLTQSPATLSVSPGERATLSC	RASQSVSS-----NLA	WYQQKPGQAPRLLIY	GASTRAT	GIPARFSGSGSGTEFTLTISSLQSEDFAVYYC	QQYNNWP-RYTFGQGTKLEIKR
RhD201.164H12	Kappa	(1) EIVLTQSPATLSVSPGERATLSC	RASQSVTS-----NLA	WYQQKPGQAPRLLIY	GASTRAT	GVPARFSGSGSGTEFSLTISSLQSEDFAVYYC	QQYNNWPPIFTFGPGTKLDIKR
RhD303.160B11	Kappa	(1) EIVLTQSPGTLSLSPGETATLSC	RASQSVSDR----DLA	WYQQKSGQSPRLLMY	GGSTRAP	GIPVFRFSGSGSGTEFTLTISSLQSEDFAIYYC	QHYHDWP--PTFGQGTRLEIKR
RhD159.119B09	Kappa	(1) EIVMTQSPGTLSLSPGERATLSC	RASHTVSSG----YLA	WYQQKPGQAPRLLIY	GASNRAT	GVPDRFGGSGSGTDFTLTISRLEPEDSAVYFC	QQYGTSP-GVTFGQGTRLEIER
RhD191.119E08	Kappa	(1) EIVLTQSPGTLSLSPRERATLSC	RASQSVTSR----YLA	WYQQKPGQAPRLLIY	GTSTRAT	GIPDRFSGSGTGTDFTLTISRLEPEDFAVYYC	QQYGSSP-LYSFGQGTKVDIKR
RhD294.119E10	Kappa	(1) EIVLTQSPGTLSLSPGERATLSC	RANQYVNSN----HLA	WYQQKPGQAPRLLIY	GASRRAT	GIPDRFSGSGTGTDFTLIISRLEPEDFAVYFC	QLYDHSRPMYTFGQGTKLEIKR
RhD202.158E07	Kappa	(1) EIVLTQSPGTLSLSPGERATLSC	RASQSVSSS----YLA	WYQHKPGQAPRLLIY	GSSNRAT	GIPDRFSGSGSGTDFTVTISRLEPEDFAVYYC	QQYGTA--PYTFGQGTKLEIKR
RhD242.181A03	Kappa	(1) EIVLTQSPGTLSLSPGERATLSC	RASQSVSSS----YLA	WYQQKPGQAPRLLIY	GASSRAT	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	QQYCGS--RYTFGQGTKLEIKR
RhD295.119B11	Kappa	(1) EIVLTQSPGTLSLSPGERATLSC	RASQSFSSG----YLA	WYQQKPGQAPRLLIY	GASNRAT	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	QHYGSSP-PITFGQGTRLEIKR
RhD317.144A02	Kappa	(1) EIVLTQSPGTLSLSPGERATLSC	RASQSVSSA----FLA	WYQQKPGQAPRLLIY	GASSRAT	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	QQYCSF--SITFGQGTRLEIKR
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RhD305.181E06	Kappa	(1) EIVLTQSPGSLSLSPGERATLSC	RASQSVSSS----YLA	WYQQKPGQAPRLLIY	GPSSRAT	GIPDRFSGSGSGTDFTLTISSLQPEDVATYYC	HTYNSAP--FAFGPGTKVDIKR
RhD163.119A02	Kappa	(1) EIVLTQSPGTLSLSPGERATLSC	RASQNPRRN----FLA	WYQQKPGQAPRLLIY	AASTRAT	GVPSRFSGGGSGTDFTLTISSLQPEDVATYYC	QKYNSAP--FAFGPGTKVDIKR
RhD306.223E11	Kappa	(1) EIVLTQSPGTLSLSPGERVTLSC	RPSRYIASD----YLA	WYQLRPGQAPKLLIY	GASSRAT	GIPDRFSGVGSPTDFTLTISRLEPEDFAMYYC	HYSGGSP-PYPFCGQGTRLDIKR
RhD301.160A04	Kappa	(1) DVVMTQSPLSLPVTPGEPASISC	RSSQSLLHRNGYNYLN	WYLQKPGQSPQLLIY	LGSNRAS	GVPDRFSGSGSGTDFTLKISGVEAEDVAFYYC	MQGLRTP--YTFGQGTKLEIKR
RhD304.164B06	Kappa	(1) DIQMTQSPSSLSASLGGTVTITC	RSSQFISR----YLN	WYQQHPGKVPRLLIS	GASRLQR	GVPSRFTGGGSGTDFTLTIKNVQPDDIATYFC	QHSYRSG--RAFGQGTTVEVKR
RhD158.119B06	Kappa	(1) DIQMTQSPSPLSASVGDRVSITC	RASRGISN----SLA	WYQQKPGKVPKLLIY	AASTLQS	GVPSRFSGGGSGTDFTLTISSLQPEDVATYYC	QQLNSYS-RWAFGQGTKVEVKR
RhD160.119C07	Kappa	(1) DIQLTQSPSSLSASVGDRVSITC	RASQGISN----SLA	WYQQKPGKVPKLLIY	GLSNLED	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC	QQYNSFP--YTFGQGTKLEFTR
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RhD161.119E09	Kappa	(1) DIQMTQSPSFLSASVGDRVTITC	RASQGIRR----YLA	WFQQKPGKAPKLLIF	SASTLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	QQLSSYP-PYTFGQGTKLEIKR
RhD205.160B12	Kappa	(1) DIQLTQSPSFLSASVGDRVTITC	RASHGISS----YLA	WYQQKPGKAPNLLIF	PASTLQS	GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC	QQLNSYS-RWAFGQGTKVEVKR
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*Numbering after amino acid 95 does not follow Clothia.

Fig. 6B

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		1	2	3		4		5	6	7	8	9	*	10 11
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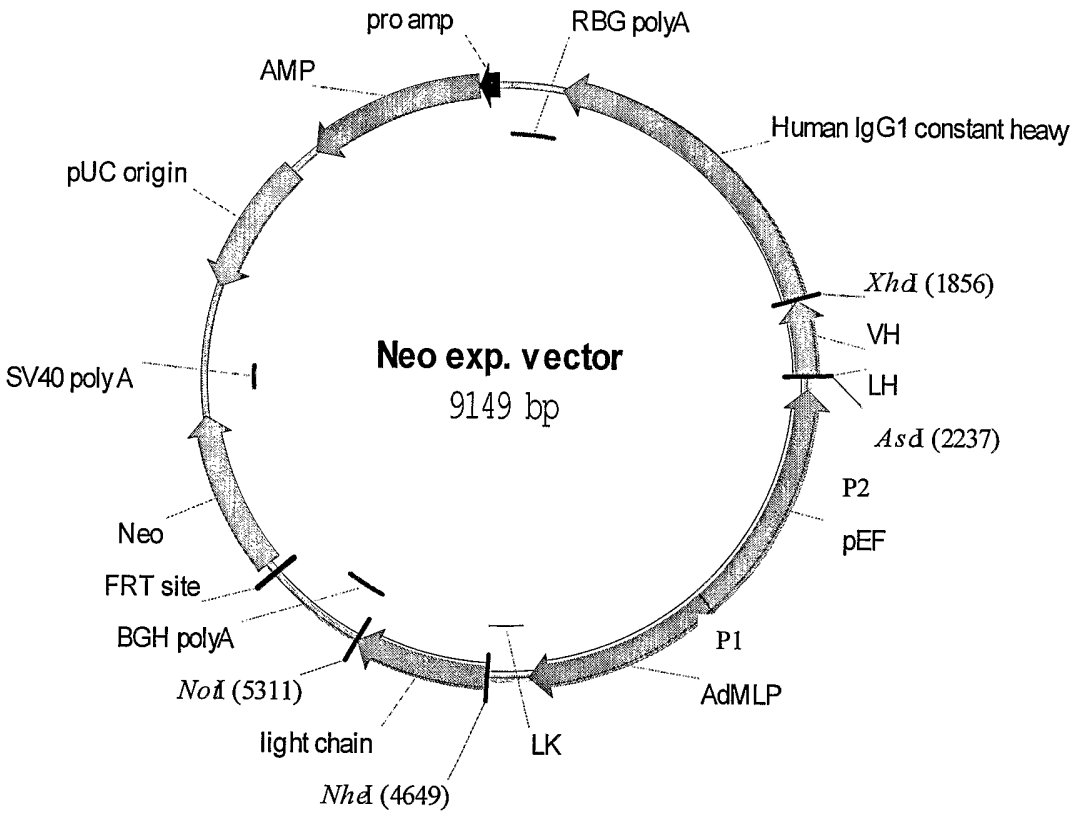
*Numbering after amino acid 95 no longer follows Clothia.

Fig. 7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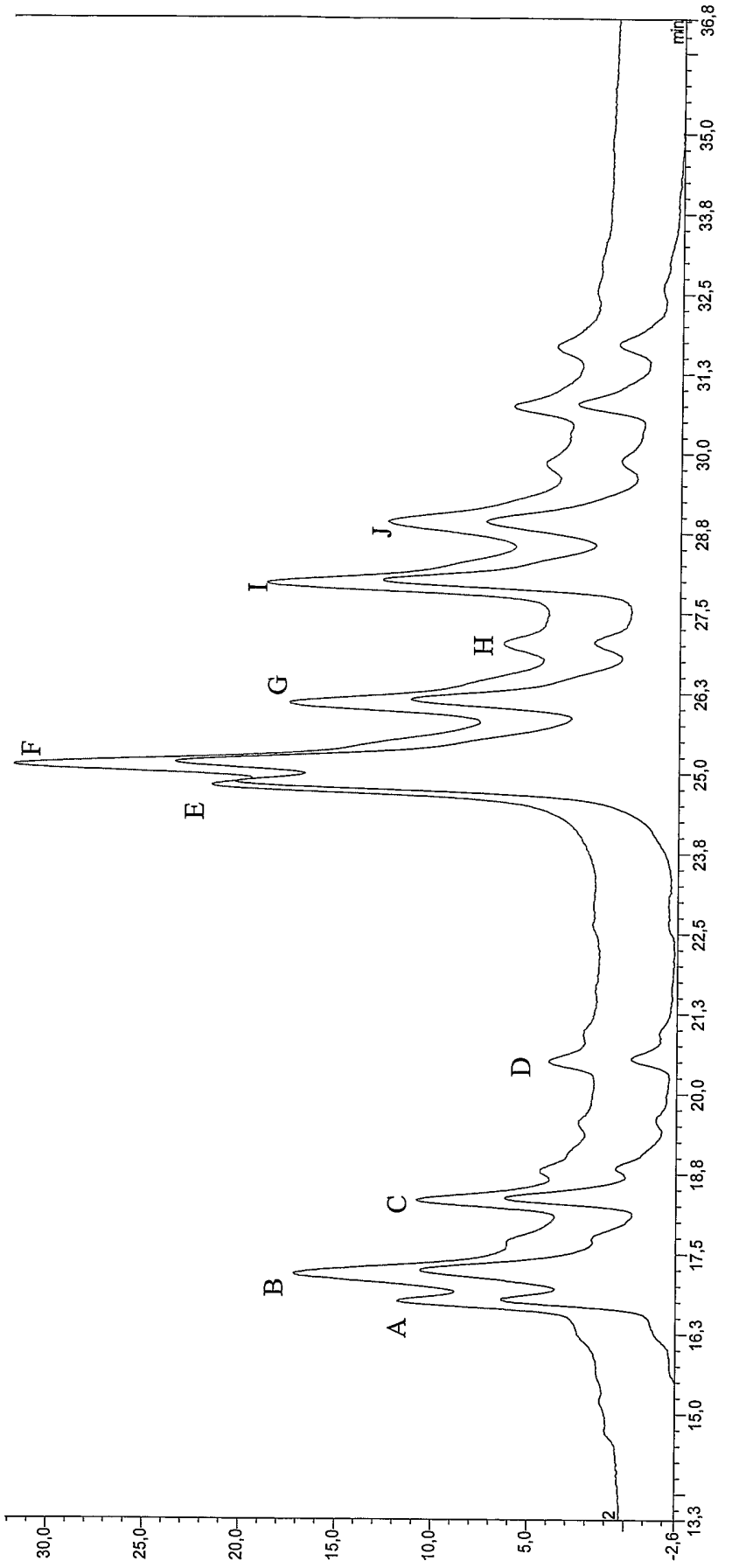
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Fig. 8

Fig. 9

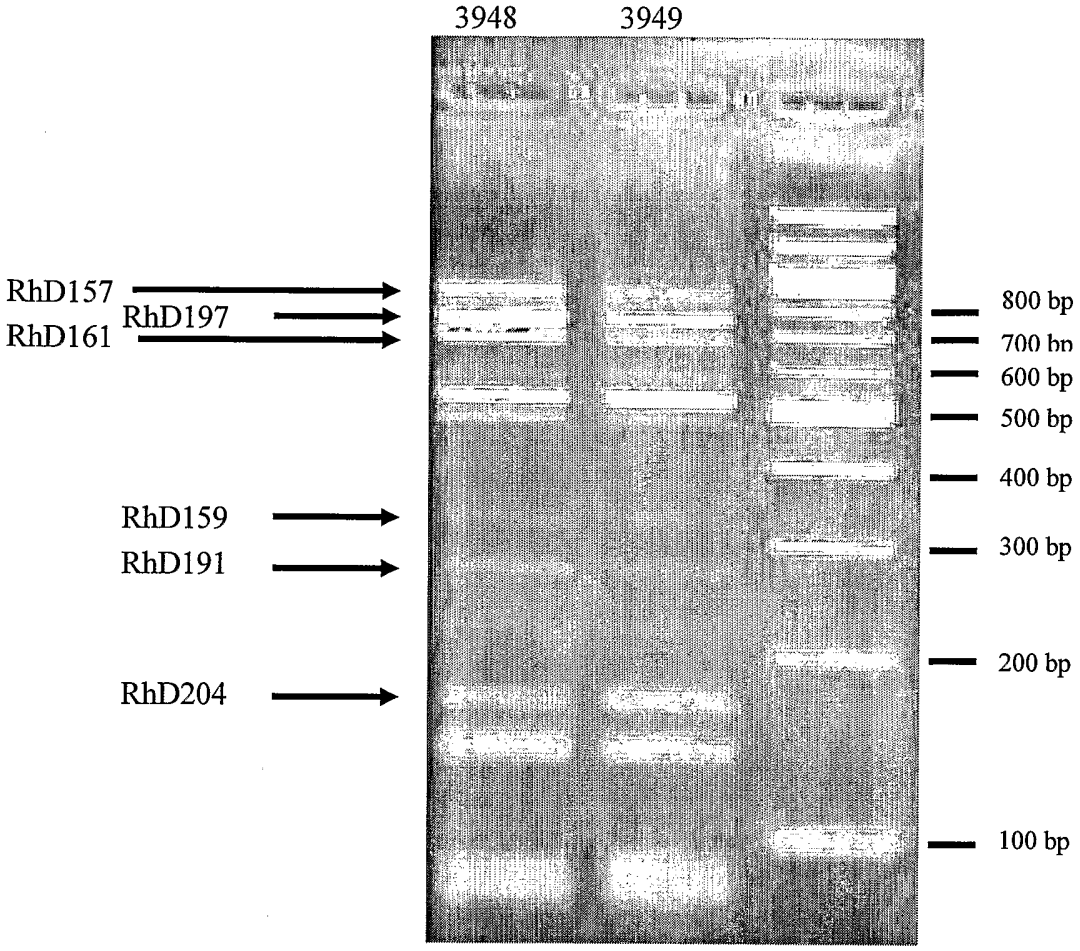
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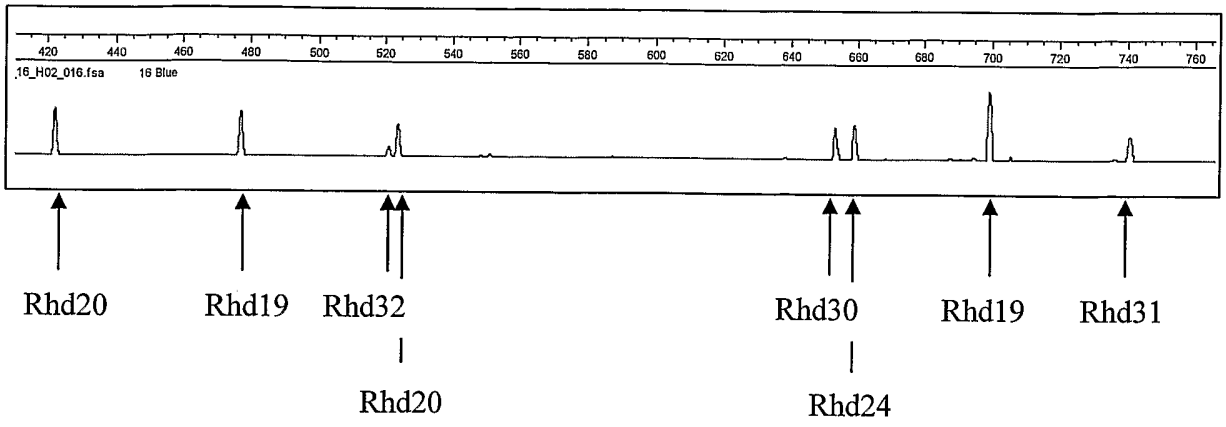
Fig. 10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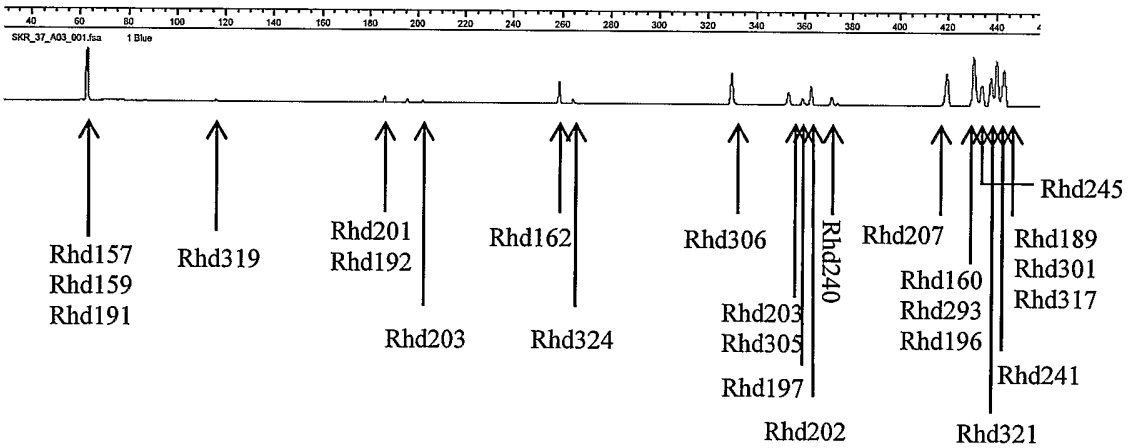
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Fig. 12

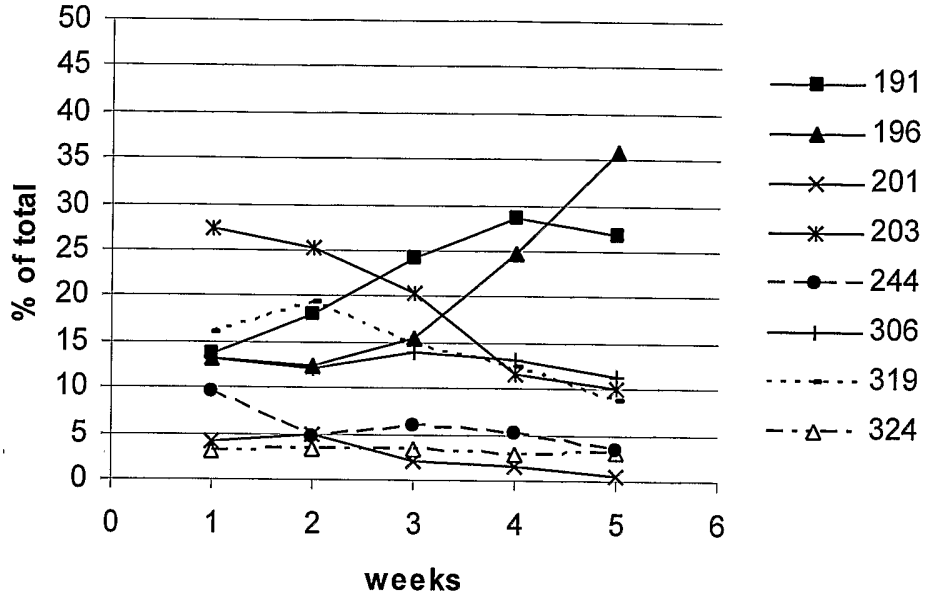
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Fig. 13

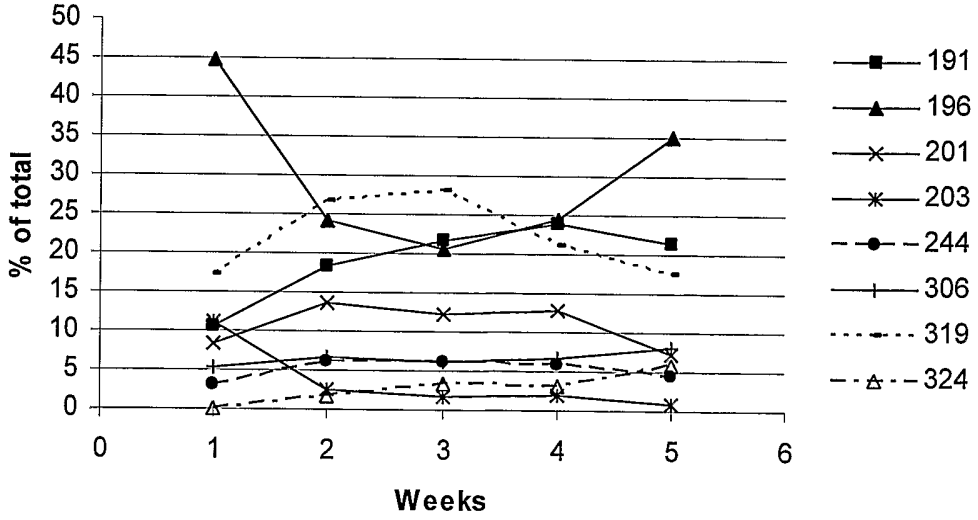
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Fig. 14

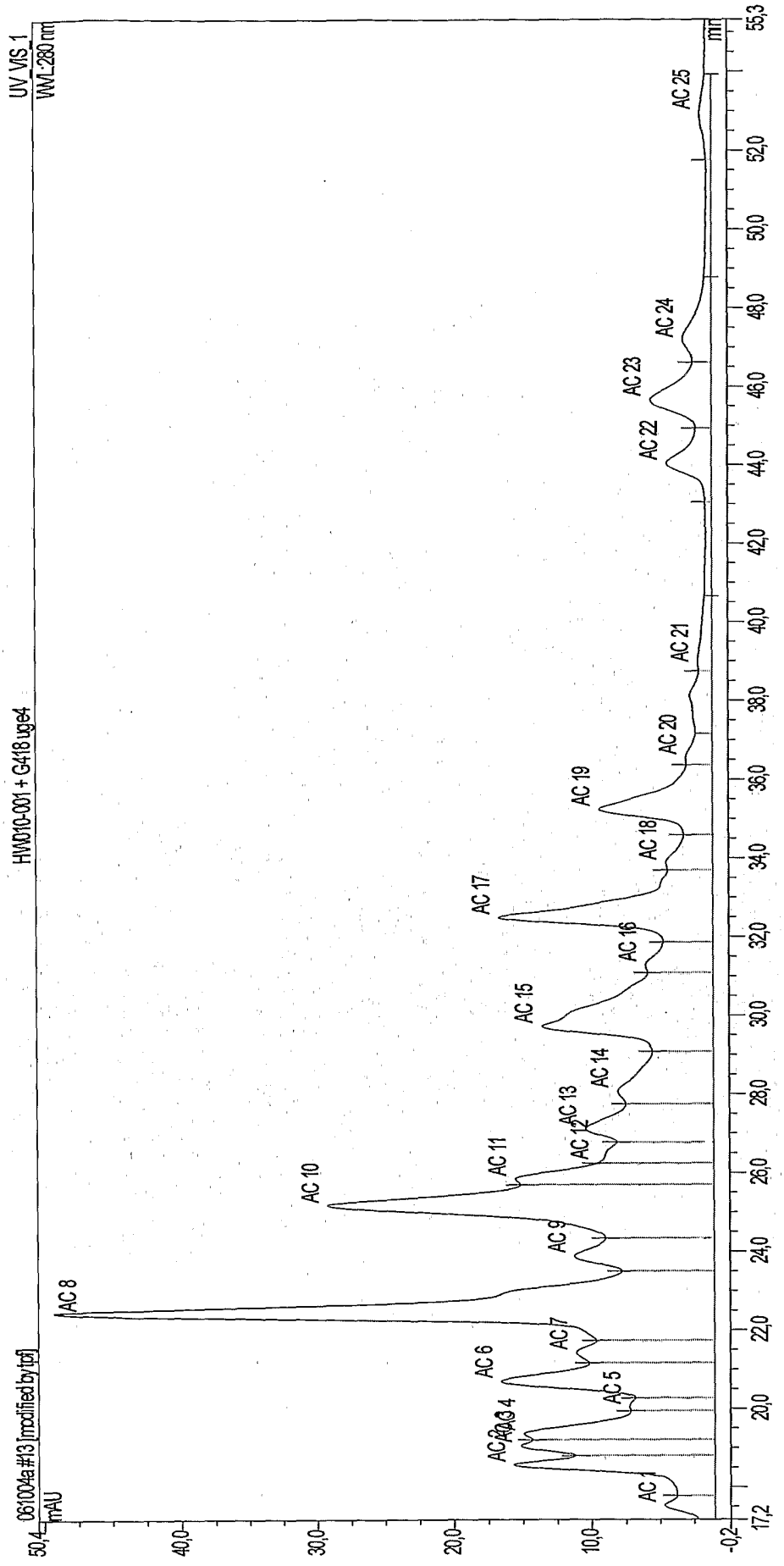
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Fig. 15

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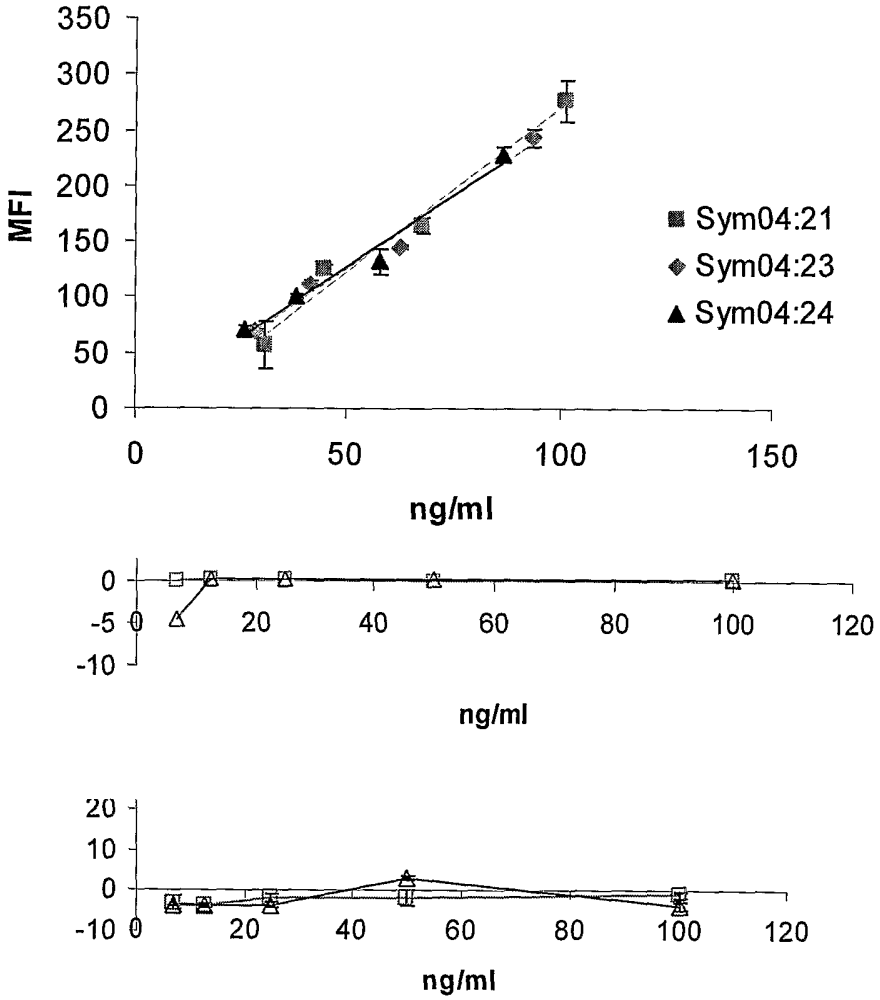
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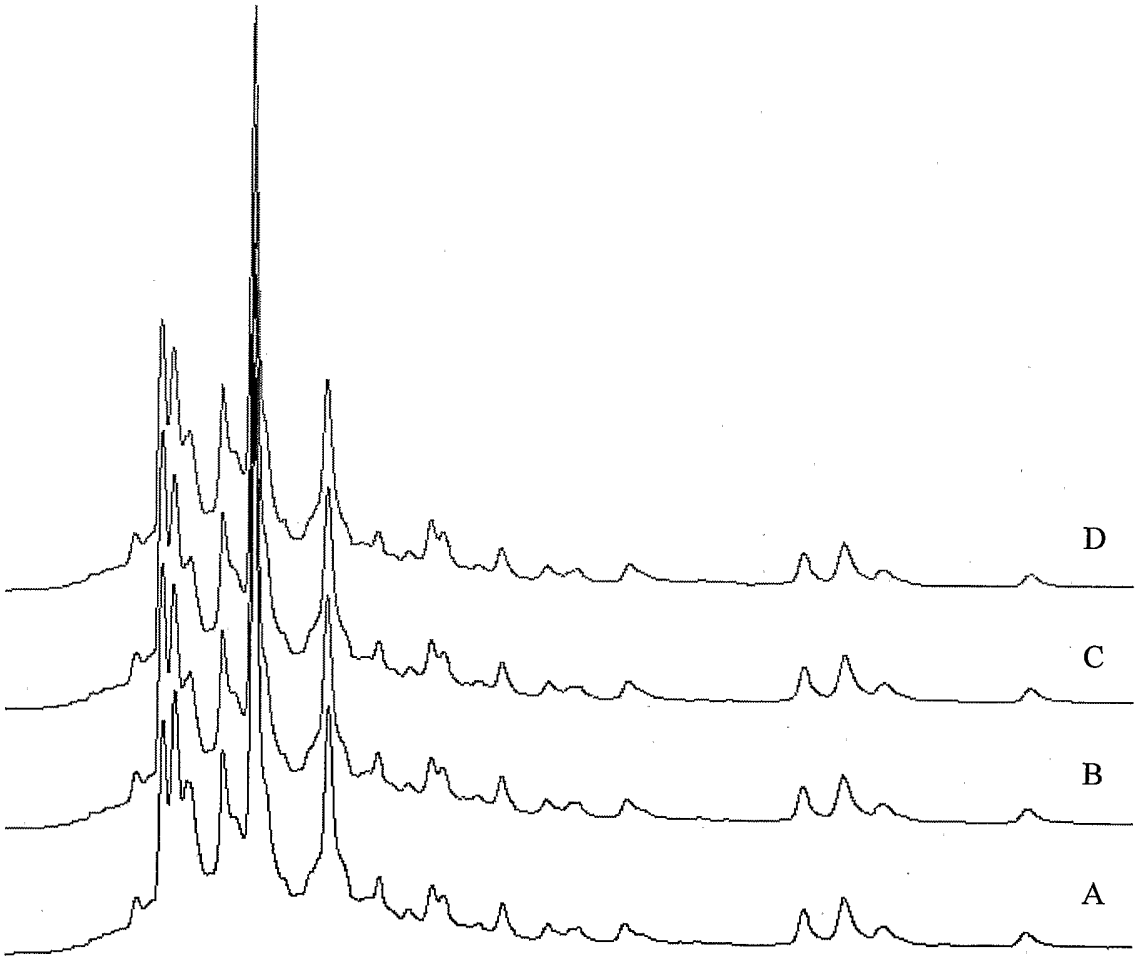
Fig. 16



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<210> 27
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<212> DNA
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<400> 27
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<210> 28
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<400> 28
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<210> 29
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<210> 30
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<400> 30
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<210> 31
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<210> 32
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<400> 32
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<400> 33
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<210> 34
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<400> 34
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<210> 35
<211> 381
<212> DNA
<213> Homo Sapiens

<400> 35
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ccagggaagg ggctggagtg ggtttcatac attaatagta ggggtagtac catatactac 180

gcagactctg tgaagggccg attcaccatc tccagagaga acgccaagaa ctcactgtat 240

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tacggtgact atgaccctaa gtcctactat tactacggta tgggcgtctg gggccaaggg 360

accacggtca ccgtctcgag t 381

<210> 36
<211> 375
<212> DNA
<213> Homo Sapiens

<400> 36
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ccaggcaagg ggctcgaatg ggtggcagtt atttggtatg atggaagcaa cagattctat 180

gcagattccg tgaagggccg attcaccatc tccagagata gttcgaagaa catgctgttt 240

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tccatgaaag tagtgatccg cagacactac gttatggacg tctggggcca cgggaccacg 360

gtcaccgtct cgagt 375

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ccagggaagg ggctggagtg ggtgtcatac atcagtggca gaggtagtac aacatattac 180

gcagactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240

ctgcaaatga acagtctgag agccgaggac acggctgttt attactgtgc gagagatttg 300

tacggtgact acgatcctaa gtcctactat tactacgcta tggacgtctg gggccacggg 360

accacggtca ccgtctcgag t 381

<210> 38
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<212> DNA
<213> Homo Sapiens

<400> 38
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ccaggcaagg ggctggagtg ggtggcggtt atatggtatg atggaagtaa tagattctat 180

gcggactccg tgaagggccg attcaccatc tccagagaca attccaagaa tacgctgtat 240

ctgcaaatga acaacctgag agccgaggac acggctctct attcctgtgc gagagagatt 300

actacgacag tagtggtccg aagacactac cttatggaca tctggggcca agggaccacg 360

gtcaccgtct cgagt 375

<210> 39
<211> 378
<212> DNA
<213> Homo Sapiens

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ccaggcaagg ggctggagtg ggtggcattt atttggtatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacactgtat 240

ctgcaaatgg acggcctgag agccgaggac tcggctgtgt attactgtgc gagagaggaa 300

atagcagctc gtctttattc tcgctaccac tacgctatgg acgtctgggg ccaagggaca 360

atggtcaccg tctcgagt 378

<210> 40
<211> 375
<212> DNA
<213> Homo Sapiens

<400> 40
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tcctgtgcag cctctggatt cggcttcagt gcttatagca tgaactgggt ccgccaggct 120

ccggggaagg ggctggagtg ggtctcatcc attactagca ctactacata ctacgcagac 180

tcagtgaagg gccgattcag catctccaga gacaacgcca agagcacact gtacctgcga 240

atgaacagcc tgagagccga ggacacggct gtatattatt gtgtgagaga aatcgccttt 300

agggggagca cttattctcg gtggtcgtac tactttgact tctggggcca gggaaccctg 360

gtcaccgtct cgagt 375

<210> 41
<211> 384
<212> DNA
<213> Homo Sapiens

<400> 41
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acctgcactg tctctggtgg ctccatcagt agttactact ggagctgggt ccggcagccc 120

ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac 180

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caatatgggt cggcgatccg aggttctcga tactactacg ggatggacgt ctggggccaa 360

gggaccacgg tcaccgtctc gagt 384

<210> 42
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 42
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagacatg 300

gttactatgg ttcggggagc ctacagaaac tactactact acggtatgga cgtctggggc 360

aaagggacca cggtcaccgt ctcgagt 387

<210> 43
<211> 381
<212> DNA
<213> Homo Sapiens

<400> 43
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tcctgtgcag cctctggatt cagcttcagt aactatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggttggagtg ggtggcagtt atttggtttg atggaagtat taaatattat 180

gtagactccg tgaaaggccg attcaccatc tccagagaca attccaagaa cacactctat 240

ctgcaaatga acagcctgag agccgaggag acggctatat atttctgtgc gagagaaaat 300

agtgttctag tcccaggtac tatacggagg cgatattatt tggactactg gggccaggga 360

accctggtca ccgtctcgag t 381

<210> 44
<211> 381
<212> DNA
<213> Homo Sapiens

<400> 44
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tcctgtgcag cctctggatt caccttcagg agttatgaaa tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtttcatac attaatagta gaggtaatac caaatactac 180

gcagactctg tgaagggccg attcaccatc tccagagaca acgccaagaa gtcactgtac 240

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ttcggtgact acgatcttaa gtcctactac tataacgcta tggacgtctg gggccaaggc 360

accctggtca ccgtctcgag t 381

<210> 45
<211> 381
<212> DNA
<213> Homo Sapiens

<400> 45
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tcctgtgcag cctctggatt caccttcagt agttatgcca tgaactgggt ccgccaggct 120

ccagggaagg gactggagtg ggtctcatcc attagcggta ctagtagtta catatactat 180

gcagactcag tgaagggccg atttaccatt ttcagagaca acgccaagag ctcagtttat 240

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tggtggggca tggttcggag agtttttccc acctatccct ttgactactg gggccaggga 360

accctggtca ccgtctcgag t 381

<210> 46
<211> 375
<212> DNA
<213> Homo Sapiens

<400> 46
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaagactat 180

gcagaccccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctcag agccgaggac acggctgtgt attactgtgc gagagagatc 300

gcctcccgtg gatatagtcg ctacttatac tactttgact cctggggcca gggaaccctg 360

gtcaccgtct cgagt 375

<210> 47
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 47
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acctgcaccg tctctgggtt ctcactcagc aatgctagaa tgggtgtgag ctggatccgt 120

cagcccccag ggaaggccct ggagtggctt gcacacattt tttcgaatga cgaaaaatcc 180

tacagcacat ctctgaagag caggctcacc atctccaagg acacctccaa aagccaggtg 240

gtccttacca tgaccaacat ggaccctgtg gacacagcca catattactg tgcacggatg 300

aggcttacta tggttcgggg agttattacg tactactact acagtatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 48
<211> 381
<212> DNA
<213> Homo Sapiens

<400> 48
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acctgcactg tctctggtgg ctccatcagc agtggtagtt actactggag ctggatccgg 120

cagcccgccg ggaagggacc ggagtggatt gggcgtatct ataccagtgg gagtaccaac 180

tacaacccct ccctcaagag tcgactcacc atatcagtag acacgtccaa gaaccagttc 240

tccctgaagc tgacctctgt gaccgccgca gacacggccg tgtattactg tgcgagggcc 300

ccttcttact atgatagtag tggttatcgt tactggtaca tcgatctctg gggccgtggc 360

accctggtca ccgtctcgag t 381

<210> 49
<211> 378
<212> DNA
<213> Homo Sapiens

<400> 49
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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gcagactccg tgaagggccg attcaccatc tccagagaca actccaagaa cacgctgtat 240

ctgcaaatga acagcgtgag agccgaggac acggctgttt attactgtgc gagagaattg 300

agcacgcaac gtggatacag ccgctaccac tatgttatgg acgtctgggg ccaagggacc 360

acggtcaccg tctcgagt 378

<210> 50
<211> 363
<212> DNA
<213> Homo Sapiens

<400> 50
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tcctgtgcag cgtctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120

cctggcaagg ggctggaatg ggtggcagtt atctggtttg atggaagtaa tagagactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa gacgctctat 240

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gccagagggc ggctacgagc cctagagtac tggggccagg gaaccctggt caccgtctcg 360

agt 363

<210> 51
<211> 378
<212> DNA
<213> Homo Sapiens

<400> 51
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tcctgtgcag cgtctggatt caccttcagt acctatggca tgcactgggt ccgccaggct 120

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gcagactccg tgaagggccg attcaccatc tccagagaca cttccaagaa cacgctgtat 240

ctgcaaatga acagcgtgag agtcgaggac acggctgttt attactgtgc gagagatttg 300

accacgcaac gtggatacag ccgctatcac tatgttatgg acgtctgggg ccaagggacc 360

acggtcaccg tctcgagt 378

<210> 52
<211> 378
<212> DNA
<213> Homo Sapiens

<400> 52
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgcat 240

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ggttttggca gtggctggtc acgatactac tacggtatgg acgtctgggg ccaagggacc 360

acggtcaccg tctcgagt 378

<210> 53
<211> 390
<212> DNA
<213> Homo Sapiens

<400> 53
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ctctcctgtg cagcgtctgg attcaccttc agtagctatg gcatgcactg ggtccgccag 120

gctccaggca aggggctgga gtgggtggca gttatatggt atgatggaag taataaatac 180

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agtactctgt atagcagcag ctggtacagg aggtactact actacggtat ggacgtctgg 360

ggccaaggga ccacggtcac cgtctcgagt 390

<210> 54
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 54
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tcctgtgcag cctctggatt caccttcagt agctatgcta tgcactgggt ccgccaggct 120

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actctatata gcagcagctg gtacaggagg tactactact acagtatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 55
<211> 384
<212> DNA
<213> Homo Sapiens

<400> 55
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tcctgtgcgg cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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tatacacgta gcgggctatg gtcacaaggg tactcctatt acatggacgt ctggggcaaa 360

gggaccacgg tcaccgtctc gagt 384

<210> 56
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<212> DNA
<213> Homo Sapiens

<400> 56
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gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

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gtctcctata gcagcagctg gtaccgccgc tactactact acgttatgga cgtctggggc 360

aaagggacca cggtcaccgt ctcgagt 387

<210> 57
<211> 369
<212> DNA
<213> Homo Sapiens

<400> 57
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ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtga gaagtactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa ggcgctgtat 240

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ggagctaccc ggcgggcagt cgttgctttt gatatctggg gccaagggac cacggtcacc 360

gtctcgagt 369

<210> 58
<211> 381
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<400> 58
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tcctgtgcag cctctggatt caccttcagg agttatagca tgaactgggt ccgccaggct 120

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cctctaaact atgattacat ttggggaggg tatcgtttca ctatccactg gggccaggga 360

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<210> 59
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<212> DNA
<213> Homo Sapiens

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tcctgtgcag cgtctggatt caccttcagt agttatggca tgcactgggt ccgccaggct 120

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ggctattata gcagcagctg gtaccgaaac tactattact acgctatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 60
<211> 363
<212> DNA
<213> Homo Sapiens

<400> 60
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tcctgtgcgg cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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gccaaagggc ggctacgaga cctagaccac tggggccagg gaaccctggt caccgtctcg 360

agt 363

<210> 61
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 61
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tcctgtgcag cctctggatt caccttcagg acttctgcca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

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gtctcctata gcagcagctg gtaccgccgc tactactact acaatatgga cgtctggggc 360

aaagggacca cggtcaccgt ctcgagt 387

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<212> DNA
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tcctgtgcag cgtctgggtt cacctttaga acctatggca tgcactgggt ccgccaggct 120

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gcctcccgtg gatatagtcg ctacttatac tactttgact cctggggcca gggcaccctg 360

gtcaccgtct cgagt 375

<210> 63
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<212> DNA
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<400> 63
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cccccaggga aggggctgga atggattggg gaaatccatc atggtgggag caccaactac 180

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caagggacaa tggtcaccgt ctcgagt 387

<210> 64
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<212> DNA
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atctgcactg tctctggtgg ctccatcagt agtaactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattgggtat atctattaca gtgggaacac caactacaac 180

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<212> DNA
<213> Homo Sapiens

<400> 65
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ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag ggccgaggac acggctgtgt attactgtgc gagagagatg 300

gcctcctata gcagcagctg gtaccgccgc tactactact acgttatgga cgtctggggc 360

aaagggacca cggtcaccgt ctcgagt 387

<210> 66
<211> 375
<212> DNA
<213> Homo Sapiens

<400> 66
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tcctgtgcag cgtctggatt caccttcagt acctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtca gaaatactat 180

gtagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

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gcggttcggg gagttattcg ctactactac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cgagt 375

<210> 67
<211> 384
<212> DNA
<213> Homo Sapiens

<400> 67
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ccaggcaagg gactggagtg ggtggcaatt atttggtatg atgggagtaa caaactctat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaggaa tacgttgtat 240

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gttcggggag tcagtagatg ggggactcag aaatattacg ctatggacgt ctggggccaa 360

gggaccacgg tcaccgtctc gagt 384

<210> 68
<211> 378
<212> DNA
<213> Homo Sapiens

<400> 68
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gcagactctg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

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cggaaccacg ttttttggag tggttattct acctcttttg actactgggg ccagggaacc 360

ctggtcaccg tctcgagt 378

<210> 69
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 69
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ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

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gtctcctata gcagcagctg gtaccgccgc tactactact acaatatgga cgtctggggc 360

aaagggacca cggtcaccgt ctcgagt 387

<210> 70
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 70
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtctg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaggaa cacgctgtat 240

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ggggggtata gcagcagttg gtaccgccgc tactactact actatatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 71
<211> 375
<212> DNA
<213> Homo Sapiens

<400> 71
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tcctgtgcag cgtctggatt caccttcaat acctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

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gcggttcggg gagttattcg ctactactac gctatggacg tctggggcca agggaccacg 360

gtcaccgtct cgagt 375

<210> 72
<211> 369
<212> DNA
<213> Homo Sapiens

<400> 72
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tcctgtgcag cctctggatt cagcttcagt aactatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtga gaagtactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa aacgctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctatgt attattgtaa gaataaagtg 300

ggagctaccc ggcgggcagt tgttgctgtt gatatttggg gccaagggac aatggtcacc 360

gtctcgagt 369

<210> 73
<211> 381
<212> DNA
<213> Homo Sapiens

<400> 73
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ccagggaagg ggctggagtg gatttcatat attaatagta gggggaacac cagatactat 180

gtagactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctcattgtat 240

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tacggtgact acgatcctaa gtcctactat tactacggta tggacgtctg gggccaaggg 360

acaatggtca ccgtctcgag t 381

<210> 74
<211> 375
<212> DNA
<213> Homo Sapiens

<400> 74
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tcctgtgaag cgtctggatt caccttcagt aattatggca tgcactggtt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcaatt atatggtatg atggaagtaa taaacactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attcgaagaa cacgctgtat 240

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gcctcccgtg gatatagtcg ctacttatac tactttgact cctggggcca gggaaccctg 360

gtcaccgtct cgagt 375

<210> 75
<211> 375
<212> DNA
<213> Homo Sapiens

<400> 75
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tcctgtgcag cgtctggatt caccttcagg acctatggca tgcactgggt ccgccaggct 120

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gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgcat 240

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gcctcccgtg gatatagtcg gtacttatac taccttgact tctggggcca gggcaccctg 360

gtcaccgtct cgagt 375

<210> 76
<211> 378
<212> DNA
<213> Homo Sapiens

<400> 76
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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agcacgcaac gtggatacag ccgctactac tatgttatgg acgtctgggg ccaagggacc 360

acggtcaccg tctcgagt 378

<210> 77
<211> 363
<212> DNA
<213> Homo Sapiens

<400> 77
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tcctgtgcag cgtctggatt caccttcagt aactttggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaagactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagag gacgctgtat 240

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gccagagggc ggctacgaga cctagactac tggggccagg gcaccctggt caccgtctcg 360

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<210> 78
<211> 384
<212> DNA
<213> Homo Sapiens

<400> 78
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagagttc 300

tatacacgta gcgggctatg gtcacaaggg tactcctatt acatggacgt ctggggcaaa 360

gggaccacgg tcaccgtctc gagt 384

<210> 79
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 79
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtttg atggaggtaa taaatactat 180

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tcggtgcttt ctggattggt tactcgaagg ttagtctact acggtatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 80
<211> 387
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<213> Homo Sapiens

<400> 80
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tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcgttt atatcatatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtct 240

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ggctattatc gcagcagctg gtaccgaaac tactactact atgggatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 81
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 81
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tcctgtgcag cctctggatt caccttcagt tcctatggca tgcactgggt ccgccaggct 120

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gtggggtata gcagcagctg gtacaggcgc tactactact acgctatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 82
<211> 384
<212> DNA
<213> Homo Sapiens

<400> 82
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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gtggtggtag ctgccaaaat acgaaaccac tactactacg ctatggacgt ctggggccaa 360

gggaccacgg tcaccgtctc gagt 384

<210> 83
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 83
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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gggggtata gcagcagttg gtaccgccgc tactactact acaatatgga cctctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 84
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 84
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

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actctgtata gcagcagctg gtacaggagg tactactact acggtatgga cgcctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 85
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 85
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tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

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cagggcaccc tggtcaccgt ctcgagt 387

<210> 86
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 86
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tcttattatg atagtagtgg ttattccttt cgcggtctgg tagcttttga tatctggggc 360

caagggacaa tggtcaccgt ctcgagt 387

<210> 87
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 87
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tcctgtgcag cgtctggatt caccttcagt acctatggca tgcactgggt ccgccaggct 120

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caagggtata gaagcagctg gtaccggatg tactactact acggtatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 88
<211> 381
<212> DNA
<213> Homo Sapiens

<400> 88
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cctctaaact atgattacat ttggggaagg tctcgtctca ctatccactg gggccaggga 360

accctggtca ccgtctcgag t 381

<210> 89
<211> 387
<212> DNA
<213> Homo Sapiens

<400> 89
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gtcactcgca gcagcaactg gtacaggaac tactactact acggtatgga cgtctggggc 360

caagggacca cggtcaccgt ctcgagt 387

<210> 90
<211> 372
<212> DNA
<213> Homo Sapiens

<400> 90
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cgacgatttt tggagtgggc ccgctacggt atggacgtct ggggccgagg gaccacggtc 360

accgtctcga gt 372

<210> 91
<211> 654
<212> DNA
<213> Homo Sapiens

<400> 91
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<210> 92
<211> 648
<212> DNA
<213> Homo Sapiens

<400> 92
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gggaaagttc ctaagctcct catctatgct gcatccactt tgcaatcagg ggtcccatct 180

cggttcagtg gcggtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagatgttg caacttatta ctgtcacacg tataacagtg ccccttcgc tttcggccct 300

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<210> 93
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<212> DNA
<213> Homo Sapiens

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ggccaaggga cacgactgga aattgaacga actgtggctg caccatctgt cttcatcttc 360

ccgccatctg atgagcagtt gaaatctggg actgcctctg ttgtgtgcct gctgaataac 420

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 480

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<210> 94
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<400> 94
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gggaaagttc ctaagctcct catctatgct gcatccactt tgcaatcagg ggtcccatct 180

cggttcagtg gcggtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

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cctgcccggt tctcaggctc cctccttggg ggcaaagctg ccctgacact gtcaggtgtg 240

cagcctgagg acgaggctga gtattactgc ctgctcttct atggtggtgc tcagctgggg 300

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aaggcgggag tggagaccac cacaccctcc aaacaaagca acaacaagta cgcggccagc 540

agctacctga gcctgacgcc tgagcagtgg aagtcccaca aaagctacag ctgccaggtc 600

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<211> 654
<212> DNA
<213> Homo Sapiens

<400> 134
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accccaggcc agcctccacg cacgctcatc cacagcacaa atactcggtc ttctggggtc 180

cctgatcgct tctctggctc catccttggg aacaaagctg ccctcaccat cacgggggcc 240

caggcagatg atgaatctga ttattactgt gtgctgtata tgggtagtgg cccttgggtg 300

ttcggcggag ggaccaagct gaccgtccta ggtcagccca aggctgcccc ctcggtcact 360

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gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540

tacctgagcc tgacgcctga gcagtggaag tcccacaaaa gctacagctg ccaggtcacg 600

catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttcata ataa 654

<210> 135

<211> 663
<212> DNA
<213> Homo Sapiens

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tacctgcaga agccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

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agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttaa 660

taa 663

<210> 136
<211> 648
<212> DNA
<213> Homo Sapiens

<400> 136
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gggaaagccc ctaagctcct gatctatgct gcatccactt tgcagagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcgctctca ccatcagcag tctgcaagct 240

gaagattttg caacttacta ctgtcaacag acttacagta ccctttggac gttcggccaa 300

gggaccaagg tggaaatcac acgaactgtg gctgcaccat ctgtcttcat cttcccgcca 360

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cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

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ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttaataa 648

<210> 137
<211> 651
<212> DNA
<213> Homo Sapiens

<400> 137
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tctggccagt ctcccagact tctcatgtat ggtggatcca ccagggcccc tggtataccg 180

gtcaggttca gtggcagtgg gtctgggaca gagttcactc tcaccatcag cagcctgcag 240

tctgaagatt ttgcaattta ttactgtcaa cactatcatg actggcctcc gaccttcggc 300

caagggacac gactggagat taaacgaact gtggctgcac catctgtctt catcttcccg 360

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480

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acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgttaata a 651

<210> 138
<211> 648
<212> DNA
<213> Homo Sapiens

<400> 138
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ctcacttgcc ggtcaagtca gttcattagt cgctatttaa attggtatca acaacaccca 120

gggaaagtcc ctagactcct catttctggc gcatcaagat tgcaaagggg ggtcccgtca 180

aggttcactg gcggcgggtc tgggacagac ttcacactca ccataaagaa tgtacagcct 240

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<211> 651
<212> DNA
<213> Homo Sapiens

<400> 139
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cctggccagg ctcccaggct cctcatctat ggtccatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcagtgta ttactgtcag cattttggta actcacgggg aacgttcggc 300

caagggacca aggtggaaat cagacgaact gtggctgcac catctgtctt catcttcccg 360

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480

caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540

acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgttaata a 651

<210> 140
<211> 654
<212> DNA
<213> Homo Sapiens

<400> 140
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cctggccagg ctcccaaact cctcatctat ggtgcctcca gcagggccac tggcatccca 180

gacaggttca gtggcgttgg gtctccgaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcgatgta ttactgtcac tattctggtg gctcacctcc gtacccttt 300

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ccgccatctg atgagcagtt gaaatctgga actgcctctg ttgtgtgcct gctgaataac 420

ttctatccca gagaggccaa agtacagtgg aaggtggata acgccctcca atcgggtaac 480

tcccaggaga gtgtcacaga gcaggacagc aaggacagca cctacagcct cagcagcacc 540

ctgacgctga gcaaagcaga ctacgagaaa cacaaagtct acgcctgcga agtcacccat 600

cagggcctga gctcgcccgt cacaaagagc ttcaacaggg gagagtgtta ataa 654

<210> 141
<211> 648
<212> DNA
<213> Homo Sapiens

<400> 141
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cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 480

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ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gttaataa 648

<210> 142
<211> 651
<212> DNA
<213> Homo Sapiens

<400> 142
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caagggacac gactggagat taaacgaact gtggctgcac catctgtctt catcttcccg 360

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480

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acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgttaata a 651

<210> 143
<211> 657
<212> DNA
<213> Homo Sapiens

<400> 143
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aaacctggac aagcacccag ggcactgatt tatagtacaa gcaacaaaca ctcctggacc 180

cctgcccggt tctcaggctc cctccttggg ggcaaagctg ccctgacact gtcaggtgtg 240

cagcctgagg acgaggctga gtattactgc ctgctctact atggtggtgc tcagcgttgg 300

gtgttcggcg gagggaccat cctgaccgtc ctaggtcagc ccaaggctgc cccctcggtc 360

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agctacctga gcctgacgcc tgagcagtgg aagtcccaca aaagctacag ctgccaggtc 600

acgcatgaag ggagcaccgt ggagaagaca gtggccccta cagaatgttc ataataa 657

<210> 144
<211> 657
<212> DNA
<213> Homo Sapiens

<400> 144
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agctacctga gcctgacgcc tgagcagtgg aagtcccaca aaagctacag ctgccaggtc 600

acgcatgaag ggagcaccgt ggagaagaca gtggccccta cagaatgttc ataataa 657

<210> 145
<211> 651
<212> DNA
<213> Homo Sapiens

<400> 145
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caagggacca aggtggaaat caaacgaact gtggctgcac catctgtctt catcttcccg 360

ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc 420

tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc 480

caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540

acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgttaata a 651

<210> 146
<211> 651
<212> DNA
<213> Homo Sapiens

<400> 146
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ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tatcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tataataact ggccccggta cacttttggc 300

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caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg 540

acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag 600

ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgttaata a 651

<210> 147
<211> 127
<212> PRT
<213> Homo Sapiens

<400> 147

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

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

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

Ser Tyr Ile Asn Ser Arg Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

```
Ala Arg Asp Leu Tyr Gly Asp Tyr Asp Pro Lys Ser Tyr Tyr Tyr Tyr
            100                 105                 110

Gly Met Gly Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210>  148
<211>  125
<212>  PRT
<213>  Homo Sapiens

<400>  148

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asn Phe
            20                  25                  30

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

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

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

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

Ala Arg Glu Ile Ser Met Lys Val Val Ile Arg Arg His Tyr Val Met
            100                 105                 110

Asp Val Trp Gly His Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210>  149
<211>  127
<212>  PRT
<213>  Homo Sapiens

<400>  149

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

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

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

Ser Tyr Ile Ser Gly Arg Gly Ser Thr Thr Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Asp Leu Tyr Gly Asp Tyr Asp Pro Lys Ser Tyr Tyr Tyr Tyr
100 105 110

Ala Met Asp Val Trp Gly His Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 150
<211> 125
<212> PRT
<213> Homo Sapiens

<400> 150

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

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

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

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

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

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

Ala Arg Glu Ile Thr Thr Thr Val Val Val Arg Arg His Tyr Leu Met
100 105 110

Asp Ile Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 151
<211> 126
<212> PRT
<213> Homo Sapiens

<400> 151

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

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

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

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

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

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

Ala Arg Glu Glu Ile Ala Ala Arg Leu Tyr Ser Arg Tyr His Tyr Ala
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120 125

<210> 152
<211> 125
<212> PRT
<213> Homo Sapiens

<400> 152

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

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

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

Ser Ser Ile Thr Ser Thr Thr Thr Tyr Tyr Ala Asp Ser Val Lys Gly
50 55 60

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

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

Glu Ile Ala Phe Arg Gly Ser Thr Tyr Ser Arg Trp Ser Tyr Tyr Phe
            100                 105                 110

Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
```

<210> 153
<211> 128
<212> PRT
<213> Homo Sapiens

<400> 153

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30

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

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

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

Arg Asp Trp Arg Gln Tyr Gly Ser Ala Ile Arg Gly Ser Arg Tyr Tyr
            100                 105                 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 154
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 154

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

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

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

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

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

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

Ala Arg Asp Met Val Thr Met Val Arg Gly Ala Tyr Arg Asn Tyr Tyr
            100                 105                 110

Tyr Tyr Gly Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser
        115                 120                 125

Ser
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<210> 155
<211> 127
<212> PRT
<213> Homo Sapiens

<400> 155

```
Glu Val Gln Leu Val Glu Thr Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

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

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

Ala Val Ile Trp Phe Asp Gly Ser Ile Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80
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Leu Gln Met Asn Ser Leu Arg Ala Glu Glu Thr Ala Ile Tyr Phe Cys
85 90 95

Ala Arg Glu Asn Ser Val Leu Val Pro Gly Thr Ile Arg Arg Arg Tyr
100 105 110

Tyr Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 156
<211> 127
<212> PRT
<213> Homo Sapiens

<400> 156

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

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

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

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

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

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

Ala Arg Asn Leu Phe Gly Asp Tyr Asp Leu Lys Ser Tyr Tyr Tyr Asn
100 105 110

Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 157
<211> 127
<212> PRT
<213> Homo Sapiens

<400> 157

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

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

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

Ser Ser Ile Ser Gly Thr Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Arg Asp Arg Trp Trp Gly Met Val Arg Arg Val Phe Pro Thr Tyr
            100                 105                 110

Pro Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
```

<210> 158
<211> 125
<212> PRT
<213> Homo Sapiens

<400> 158

```
Gln Val Gln Leu Val Glu Thr Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

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

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

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

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

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

Ala Arg Glu Ile Ala Ser Arg Gly Tyr Ser Arg Tyr Leu Tyr Tyr Phe
            100                 105                 110
```

```
Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125


<210>  159
<211>  129
<212>  PRT
<213>  Homo Sapiens

<400>  159

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


Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Ala
            20                  25                  30


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


Trp Leu Ala His Ile Phe Ser Asn Asp Glu Lys Ser Tyr Ser Thr Ser
    50                  55                  60


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


Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95


Cys Ala Arg Met Arg Leu Thr Met Val Arg Gly Val Ile Thr Tyr Tyr
            100                 105                 110


Tyr Tyr Ser Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
        115                 120                 125


Ser



<210>  160
<211>  127
<212>  PRT
<213>  Homo Sapiens

<400>  160

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


Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30
```

Ser Tyr Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Pro Glu
35 40 45

Trp Ile Gly Arg Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser
50 55 60

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

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

Cys Ala Arg Ala Pro Ser Tyr Tyr Asp Ser Ser Gly Tyr Arg Tyr Trp
100 105 110

Tyr Ile Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 161
<211> 126
<212> PRT
<213> Homo Sapiens

<400> 161

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

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

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

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

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

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

Ala Arg Glu Leu Ser Thr Gln Arg Gly Tyr Ser Arg Tyr His Tyr Val
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 162
<211> 121
<212> PRT
<213> Homo Sapiens

<400> 162

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

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

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

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

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

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

Ala Thr Glu Leu Ala Arg Gly Arg Leu Arg Ala Leu Glu Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 163
<211> 126
<212> PRT
<213> Homo Sapiens

<400> 163

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

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

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

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

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

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

Ala Arg Asp Leu Thr Thr Gln Arg Gly Tyr Ser Arg Tyr His Tyr Val
            100                 105                 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 164
<211> 126
<212> PRT
<213> Homo Sapiens

<400> 164

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

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

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

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

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

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

Ala Arg Glu Val Gly Phe Gly Ser Gly Trp Ser Arg Tyr Tyr Tyr Gly
            100                 105                 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 165
<211> 130
<212> PRT
<213> Homo Sapiens

<400> 165

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Gly Val Val Gln Pro Gly
```

1 5 10 15

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

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

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

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

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

Cys Ala Arg Glu Ser Thr Leu Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr
100 105 110

Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
115 120 125

Ser Ser
130

<210> 166
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 166

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

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

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

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

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

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

Ala Arg Glu Ser Thr Leu Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
100 105 110

Tyr Tyr Ser Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 167
<211> 128
<212> PRT
<213> Homo Sapiens

<400> 167

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

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

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

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

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

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

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

Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 168
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 168

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

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

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

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

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

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

Ala Arg Glu Met Val Ser Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
            100                 105                 110

Tyr Tyr Val Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser
        115                 120                 125

Ser
```

<210> 169
<211> 123
<212> PRT
<213> Homo Sapiens

<400> 169

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

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

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

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

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

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

Lys Asn Lys Val Gly Ala Thr Arg Arg Ala Val Val Ala Phe Asp Ile
100 105 110

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

<210> 170
<211> 127
<212> PRT
<213> Homo Sapiens

<400> 170

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

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

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

Ser Ser Ile Gly Ser Ser Ser Thr Tyr Thr Tyr Ser Ala Asp Ser Val
50 55 60

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

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

Ala Arg Gly Glu Pro Leu Asn Tyr Asp Tyr Ile Trp Gly Gly Tyr Arg
100 105 110

Phe Thr Ile His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 171
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 171

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

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

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

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

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

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

Ala Lys Glu His Gly Tyr Tyr Ser Ser Ser Trp Tyr Arg Asn Tyr Tyr
100 105 110

Tyr Tyr Ala Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 172
<211> 121
<212> PRT
<213> Homo Sapiens

<400> 172

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

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

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

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

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

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

Ala Arg Glu Leu Ala Lys Gly Arg Leu Arg Asp Leu Asp His Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 173
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 173

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

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

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

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

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

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

Ala Arg Glu Met Val Ser Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
100 105 110

Tyr Tyr Asn Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 174
<211> 125
<212> PRT
<213> Homo Sapiens

<400> 174

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

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

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

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

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

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

Ala Arg Glu Ile Ala Ser Arg Gly Tyr Ser Arg Tyr Leu Tyr Tyr Phe
100 105 110

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 175
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 175

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Met Arg Ser Ser
20 25 30

Asn Trp Trp Thr Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp
35 40 45

Ile Gly Glu Ile His His Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu
50 55 60

Gln Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Arg Phe Ser
65 70 75 80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr His Cys
85 90 95

Ala Arg Gly Arg Ser Tyr Tyr Asp Ser Ser Gly His Ser Phe Arg Gly
100 105 110

Leu Val Pro Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
115 120 125

Ser

<210> 176
<211> 128
<212> PRT
<213> Homo Sapiens

<400> 176

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

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

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

Gly Tyr Ile Tyr Tyr Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Glu Trp Arg Gln Tyr Gly Ser Gly Ile Arg Gly Ser Arg Tyr Tyr
100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 177
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 177

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn His
20 25 30

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

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

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

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

Ala Arg Glu Met Ala Ser Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
            100                 105                 110

Tyr Tyr Val Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser
        115                 120                 125

Ser
```

<210> 178
<211> 125
<212> PRT
<213> Homo Sapiens

<400> 178

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

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

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

Ala Val Ile Trp Tyr Asp Gly Ser Gln Lys Tyr Tyr Val Asp Ser Val
    50                  55                  60

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

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

Ala Arg Glu Val Ala Val Arg Gly Val Ile Arg Tyr Tyr Tyr Gly Met
            100                 105                 110
```

```
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210>  179
<211>  128
<212>  PRT
<213>  Homo Sapiens

<400>  179

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


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


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


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


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


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


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


Tyr Ala Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210>  180
<211>  126
<212>  PRT
<213>  Homo Sapiens

<400>  180

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


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


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

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

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

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

Ala Arg Asp Leu Arg Asn His Val Phe Trp Ser Gly Tyr Ser Thr Ser
100 105 110

Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 181
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 181

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

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

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

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

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

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

Ala Arg Glu Met Val Ser Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
100 105 110

Tyr Tyr Asn Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 182
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 182

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

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

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

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

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

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

Ala Arg Glu Gln Gly Gly Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
100 105 110

Tyr Tyr Tyr Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 183
<211> 125
<212> PRT
<213> Homo Sapiens

<400> 183

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

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

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

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

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

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

Ala Arg Glu Val Ala Val Arg Gly Val Ile Arg Tyr Tyr Tyr Ala Met
            100                 105                 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 184
<211> 123
<212> PRT
<213> Homo Sapiens

<400> 184

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

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

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

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

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

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

Lys Asn Lys Val Gly Ala Thr Arg Arg Ala Val Val Ala Val Asp Ile
            100                 105                 110

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

<210> 185
<211> 127
<212> PRT
<213> Homo Sapiens

<400> 185

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

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

Asp Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ser Tyr Ile Asn Ser Arg Gly Asn Thr Arg Tyr Tyr Val Asp Ser Val
50 55 60

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

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

Ala Arg Asp Leu Tyr Gly Asp Tyr Asp Pro Lys Ser Tyr Tyr Tyr Tyr
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120 125

<210> 186
<211> 125
<212> PRT
<213> Homo Sapiens

<400> 186

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

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

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

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

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

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

Ala Arg Glu Ile Ala Ser Arg Gly Tyr Ser Arg Tyr Leu Tyr Tyr Phe
            100                 105                 110

Asp Ser Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
```

<210> 187
<211> 125
<212> PRT
<213> Homo Sapiens

<400> 187

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

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

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

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

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

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

Ala Arg Glu Ile Ala Ser Arg Gly Tyr Ser Arg Tyr Leu Tyr Tyr Leu
            100                 105                 110

Asp Phe Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120                 125
```

<210> 188
<211> 126
<212> PRT
<213> Homo Sapiens

<400> 188

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

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

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

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

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

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

Ala Arg Asp Leu Ser Thr Gln Arg Gly Tyr Ser Arg Tyr Tyr Tyr Val
            100                 105                 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> 189
<211> 121
<212> PRT
<213> Homo Sapiens

<400> 189

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

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

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

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

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

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

Ala Arg Glu Leu Ala Arg Gly Arg Leu Arg Asp Leu Asp Tyr Trp Gly
            100                 105                 110
```

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 190
<211> 128
<212> PRT
<213> Homo Sapiens

<400> 190

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

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

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

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

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

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

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

Tyr Tyr Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 191
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 191

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

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

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

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

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

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

Ala Arg Asp Ala Ser Val Leu Ser Gly Leu Val Thr Arg Arg Leu Val
100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 192
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 192

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

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

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

Ala Phe Ile Ser Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Lys Glu His Gly Tyr Tyr Arg Ser Ser Trp Tyr Arg Asn Tyr Tyr
100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 193
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 193

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

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

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

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

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

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

Ala Lys Asp Glu Val Gly Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
100 105 110

Tyr Tyr Ala Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 194
<211> 128
<212> PRT
<213> Homo Sapiens

<400> 194

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

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

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

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

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

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

Ala Arg Glu Thr Val Val Val Ala Ala Lys Ile Arg Asn His Tyr Tyr
            100                 105                 110

Tyr Ala Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125


<210>  195
<211>  129
<212>  PRT
<213>  Homo Sapiens

<400>  195

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

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

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

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

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

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

Ala Arg Glu Gln Gly Gly Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
            100                 105                 110

Tyr Tyr Asn Met Asp Leu Trp Gly Gln Gly Thr Thr Val Thr Val Ser
        115                 120                 125
```

Ser

<210> 196
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 196

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

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

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

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

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

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

Ala Arg Glu Gly Thr Leu Tyr Ser Ser Ser Trp Tyr Arg Arg Tyr Tyr
100 105 110

Tyr Tyr Gly Met Asp Ala Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 197
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 197

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

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

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

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

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

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

Ala Arg Glu His Gly Gly Ser Arg Ser Gly Trp Tyr Thr Leu Arg Leu
            100                 105                 110

Ala Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
        115                 120                 125

Ser
```

<210> 198
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 198

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

Thr Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Arg Gly Ser
            20                  25                  30

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

Ile Gly Glu Ile His His Gly Gly Ser Thr Asn Tyr Asn Pro Ser Leu
    50                  55                  60

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

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Gly Thr Ser Tyr Tyr Asp Ser Ser Gly Tyr Ser Phe Arg Gly
            100                 105                 110
```

Leu Val Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
115 120 125

Ser

<210> 199
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 199

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

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

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

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

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

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

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

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 200
<211> 127
<212> PRT
<213> Homo Sapiens

<400> 200

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

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

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

Ser Ser Ile Gly Ser Ser Ser Ile Tyr Thr Tyr Ser Ala Asp Ser Val
50 55 60

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

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

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

Leu Thr Ile His Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120 125

<210> 201
<211> 129
<212> PRT
<213> Homo Sapiens

<400> 201

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

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

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

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

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

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

Ala Arg Asp Trp Val Thr Arg Ser Ser Asn Trp Tyr Arg Asn Tyr Tyr
100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
115 120 125

Ser

<210> 202
<211> 124
<212> PRT
<213> Homo Sapiens

<400> 202

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

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

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

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

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

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

Ala Arg Asp Pro Arg Arg Phe Leu Glu Trp Ala Arg Tyr Gly Met Asp
100 105 110

Val Trp Gly Arg Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 203
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 203

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

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

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

Phe Asn Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Ser Trp Pro Pro
                85                  90                  95

Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val
            100                 105                 110

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

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

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

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

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 204
<211> 214
<212> PRT
<213> Homo Sapiens

<400> 204

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

Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Arg Gly Ile Ser Asn Ser
            20                  25                  30
```

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

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

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

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

Ala Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

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

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

Phe Asn Arg Gly Glu Cys
    210
```

<210> 205
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 205

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser His Thr Val Ser Ser Gly
            20                  25                  30
```

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

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

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

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

Gly Val Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Glu Arg Thr Val
100 105 110

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

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
130 135 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145 150 155 160

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

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

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
195 200 205

Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 206
<211> 214
<212> PRT
<213> Homo Sapiens

<400> 206

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

Asp Arg Val Ser Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Ser
20 25 30

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

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

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

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

Ala Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 207
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 207

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

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

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

Phe Ser Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Leu Ser Ser Tyr Pro Pro
                85                  90                  95

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 208
<211> 214
<212> PRT
<213> Homo Sapiens

<400> 208

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

Asp Ser Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Val Ser Gly Trp
            20                  25                  30
```

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

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

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

Glu Asp Leu Ala Thr Tyr Tyr Cys Leu Gln Ala Asn Arg Phe Pro Leu
85 90 95

Ser Phe Gly Gly Gly Thr Arg Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 209
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 209

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

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

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

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

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

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

Leu Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Met Lys Arg Thr Val
            100                 105                 110

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

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

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

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

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 210
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 210

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

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

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

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

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

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

Leu Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val
100 105 110

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

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
130 135 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145 150 155 160

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

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

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
195 200 205

Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 211
<211> 214
<212> PRT
<213> Homo Sapiens

<400> 211

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

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

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

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

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

Glu Asp Ser Ala Thr Phe Tyr Cys Gln Gln Thr Tyr Ser Pro Pro Tyr
                85                  90                  95

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

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

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

Phe Asn Arg Gly Glu Cys
    210
```

<210> 212
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 212

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

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

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

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

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

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

Ser Thr Tyr Ile Phe Gly Pro Gly Thr Glu Leu Glu Ile Lys Arg Thr
            100                 105                 110

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
        115                 120                 125

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
    130                 135                 140

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145                 150                 155                 160

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

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

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

Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 213
<211> 214
<212> PRT
<213> Homo Sapiens

<400> 213

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Asn Asn Leu
            20                  25                  30
```

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 214
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 214

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

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

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Leu Ala
                85                  90                  95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  215
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  215

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

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

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

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

Ser Gly Ser Gly Thr His Phe Thr Leu Thr Ile Ser Ser Leu Gln Arg
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Arg Thr Pro Thr
                85                  90                  95

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

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  216
<211>  213
<212>  PRT
<213>  Homo Sapiens

<400>  216

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

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

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Arg Gly Thr
                85                  90                  95

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

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

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

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

Asn Arg Gly Glu Cys
    210

<210>  217
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  217

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

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

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

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

Ser Gly Ser Gly Thr His Phe Thr Leu Thr Ile Ser Ser Leu Gln Arg
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Gly Thr Pro Thr
                85                  90                  95

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

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 218
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 218

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

Thr Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Thr Gly
            20                  25                  30
```

```
Tyr Tyr Pro Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Ala
        35                  40                  45

Leu Ile Tyr Ser Thr Ser Lys Lys His Ser Trp Thr Pro Ala Arg Phe
    50                  55                  60

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

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

Ala Gln Leu Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215


<210>  219
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  219

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Asn Tyr
            20                  25                  30
```

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

Ser Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  220
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  220

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

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

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  221
<211>  214
<212>  PRT
<213>  Homo Sapiens

<400>  221

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

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

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

Phe Asn Arg Gly Glu Cys
    210
```

<210> 222
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 222

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

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

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

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

Ser Gly Ser Gly Thr Glu Phe Ser Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

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

Ile Phe Thr Phe Gly Pro Gly Thr Lys Leu Asp Ile Lys Arg Thr Val
            100                 105                 110

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

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

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

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

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 223
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 223

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

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

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

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Thr Ala Pro
85 90 95

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
100 105 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 224
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 224

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

Ser Ile Thr Ile Ser Cys Thr Ala Thr Ser Ser Asp Ile Gly Ala Tyr
20 25 30

```
Asn Tyr Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Val
        35                  40                  45

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

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

Gln Pro Glu Asp Glu Ala Glu Tyr Ser Cys Cys Ser Tyr Ala Gly Thr
                85                  90                  95

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

Pro Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys
145                 150                 155                 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 225
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 225

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

Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr
            20                  25                  30
```

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

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

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

Glu Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn
                85                  90                  95

Tyr Arg Glu Leu Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

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

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Ala Glu Cys Ser
    210                 215
```

<210> 226
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 226

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser His Gly Ile Ser Ser Tyr
            20                  25                  30
```

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

Phe Pro Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Trp Ala Phe Gly Gln Gly Thr Lys Val Glu Val Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 227
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 227

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Gln Gly
85 90 95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 228
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 228

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

Thr Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Thr Gly
20 25 30

```
Tyr Tyr Pro Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Ala
        35                  40                  45

Leu Val His Ser Thr Ser Lys Lys His Ser Trp Thr Pro Ala Arg Phe
    50                  55                  60

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

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

Ala Gln Leu Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Ala Glu Cys Ser
    210                 215
```

<210> 229
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 229

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

Thr Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ser Val Thr Ser Gly
            20                  25                  30
```

```
Tyr Tyr Pro Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Pro
        35                  40                  45

Leu Ile Ser Gly Thr Ser Asn Lys Leu Ser Trp Thr Pro Ala Arg Phe
    50                  55                  60

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

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

Pro Gln Pro Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215

<210>  230
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  230

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

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

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

Ser Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  231
<211>  214
<212>  PRT
<213>  Homo Sapiens

<400>  231

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20                  25                  30
```

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

Tyr Lys Thr Ser Ser Leu Glu Gly Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Phe Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Phe Thr Arg Thr Val Ala Ala
100 105 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 232
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 232

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

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

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

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

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

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

Leu Tyr Ser Phe Gly Gln Gly Thr Lys Val Asp Ile Lys Arg Thr Val
            100                 105                 110

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

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
    130                 135                 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145                 150                 155                 160

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

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

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
        195                 200                 205

Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 233
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 233

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

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

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

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

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

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

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
100 105 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 234
<211> 214
<212> PRT
<213> Homo Sapiens

<400> 234

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

Asp Arg Val Ile Ile Thr Cys Arg Ser Gly Gln Gly Ile Arg Asn Tyr
20 25 30

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

Tyr Ala Ala Ser Phe Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

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

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

Phe Asn Arg Gly Glu Cys
    210

<210>  235
<211>  213
<212>  PRT
<213>  Homo Sapiens

<400>  235

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Gly Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Arg Thr
                85                  90                  95

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

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

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

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

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

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

Asn Arg Gly Glu Cys
    210

<210>  236
<211>  214
<212>  PRT
<213>  Homo Sapiens

<400>  236

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

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

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

Tyr Ala Ala Ser Arg Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys Arg Thr Val Ala Ala
            100                 105                 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

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

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

Phe Asn Arg Gly Glu Cys
    210
```

<210> 237
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 237

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

Gln Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg His Ser Tyr
            20                  25                  30
```

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

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

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

Glu Asp Gly Gly Asp Tyr Tyr Cys Asn Ser Arg Asp Thr Ser Thr Asp
                85                  90                  95

His Tyr Val Phe Gly Asp Gly Thr Arg Val Thr Val Val Gly Gln Pro
            100                 105                 110

Lys Ala Asn Pro Thr Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Gly Ser Pro Val Lys Ala
145                 150                 155                 160

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

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205

Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 238
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 238

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
            20                  25                  30
```

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

Phe Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  239
<211>  214
<212>  PRT
<213>  Homo Sapiens

<400>  239

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

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

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

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

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

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 240
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 240

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

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

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

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

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

Pro Glu Asp Phe Ala Val Tyr Phe Cys Gln Leu Tyr Asp His Ser Arg
85 90 95

Pro Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr
100 105 110

Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu
115 120 125

Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro
130 135 140

Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly
145 150 155 160

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

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

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

Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 241
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 241

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Phe Ser Ser Gly
20 25 30

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

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

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

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

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

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

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
130 135 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145 150 155 160

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

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

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
195 200 205

Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 242
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 242

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

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

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

Phe Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Leu Ala
                85                  90                  95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  243
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  243

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

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

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Leu Ala
                85                  90                  95

Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215
```

<210> 244
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 244

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

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

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

Ser Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

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

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
            100                 105                 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  245
<211>  217
<212>  PRT
<213>  Homo Sapiens

<400>  245

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

Thr Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Thr Gly
            20                  25                  30
```

```
Tyr Tyr Pro Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Ala
        35                  40                  45

Leu Ile Tyr Ser Thr Ser Lys Lys His Ser Trp Thr Pro Ala Arg Phe
    50                  55                  60

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

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

Ala Gln Leu Gly Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 246
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 246

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

Thr Val Thr Leu Thr Cys Gly Leu Ser Ser Gly Ser Val Ser Ala Arg
            20                  25                  30
```

```
Tyr Tyr Pro Ser Trp Tyr Gln Gln Thr Pro Gly Gln Pro Pro Arg Thr
        35                  40                  45

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

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

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

Gly Pro Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

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

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

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

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
```

<210> 247
<211> 219
<212> PRT
<213> Homo Sapiens

<400> 247

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

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

```
Asn Gly Tyr Asn Tyr Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

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

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

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

Leu Arg Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

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

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
        195                 200                 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215

<210>  248
<211>  214
<212>  PRT
<213>  Homo Sapiens

<400>  248

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

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

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

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

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

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

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

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> 249
<211> 215
<212> PRT
<213> Homo Sapiens

<400> 249

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
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Glu Thr Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Asp Arg
20 25 30

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

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

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65                  70                  75                  80

Ser Glu Asp Phe Ala Ile Tyr Tyr Cys Gln His Tyr His Asp Trp Pro
                85                  90                  95

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

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 250
<211> 214
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<213> Homo Sapiens

<400> 250

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1               5                   10                  15

Gly Thr Val Thr Leu Thr Cys Arg Ser Ser Gln Phe Ile Ser Arg Tyr
            20                  25                  30
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Leu Asn Trp Tyr Gln Gln His Pro Gly Lys Val Pro Arg Leu Leu Ile
        35                  40                  45

Ser Gly Ala Ser Arg Leu Gln Arg Gly Val Pro Ser Arg Phe Thr Gly
    50                  55                  60

Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Lys Asn Val Gln Pro
65                  70                  75                  80

Asp Asp Ile Ala Thr Tyr Phe Cys Gln His Ser Tyr Arg Ser Gly Arg
                85                  90                  95

Ala Phe Gly Gln Gly Thr Thr Val Glu Val Lys Arg Thr Val Ala Ala
            100                 105                 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

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

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

Phe Asn Arg Gly Glu Cys
    210


<210>  251
<211>  215
<212>  PRT
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<400>  251

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

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

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

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

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln His Phe Gly Asn Ser Arg
                85                  90                  95

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

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 252
<211> 216
<212> PRT
<213> Homo Sapiens

<400> 252

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

Glu Arg Val Thr Leu Ser Cys Arg Pro Ser Arg Tyr Ile Ala Ser Asp
            20                  25                  30
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Tyr Leu Ala Trp Tyr Gln Leu Arg Pro Gly Gln Ala Pro Lys Leu Leu
35 40 45

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

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

Pro Glu Asp Phe Ala Met Tyr Tyr Cys His Tyr Ser Gly Gly Ser Pro
85 90 95

Pro Tyr Pro Phe Gly Gln Gly Thr Arg Leu Asp Ile Lys Arg Thr Val
100 105 110

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

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
130 135 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145 150 155 160

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

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

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
195 200 205

Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 253
<211> 214
<212> PRT
<213> Homo Sapiens

<400> 253

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

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

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

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ser Phe Thr Val Pro Arg
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Val Lys Arg Thr Val Ala Ala
            100                 105                 110

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

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

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

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

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

Phe Asn Arg Gly Glu Cys
    210

<210>  254
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  254

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

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

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

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

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

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

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

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> 255
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 255

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

Thr Val Thr Leu Thr Cys Ala Ser Ser Thr Gly Ala Val Thr Ser Gly
            20                  25                  30
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```
Tyr Tyr Pro Asn Trp Phe Gln Gln Lys Pro Gly Gln Ala Pro Arg Ala
        35                  40                  45

Leu Ile Tyr Ser Thr Ser Asn Lys His Ser Trp Thr Pro Ala Arg Phe
    50                  55                  60

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

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Leu Leu Tyr Tyr Gly Gly
                85                  90                  95

Ala Gln Arg Trp Val Phe Gly Gly Gly Thr Ile Leu Thr Val Leu Gly
            100                 105                 110

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
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<210> 256
<211> 217
<212> PRT
<213> Homo Sapiens

<400> 256

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Leu Asn Phe Met Leu Thr Gln Pro His Ser Val Ser Glu Ser Pro Gly
1               5                   10                  15

Lys Thr Val Thr Ile Ser Cys Thr Arg Ser Ser Gly Ser Ile Ala Ser
            20                  25                  30
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Asn Tyr Met Gln Trp Tyr Gln Gln Arg Pro Gly Ser Ser Pro Thr Thr
        35                  40                  45

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

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

Gly Leu Lys Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp
                85                  90                  95

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

Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
        115                 120                 125

Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
    130                 135                 140

Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val
145                 150                 155                 160

Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
                165                 170                 175

Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
            180                 185                 190

His Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
        195                 200                 205

Lys Thr Val Ala Pro Thr Glu Cys Ser
    210                 215

<210>  257
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  257

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30
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```
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Arg Thr Pro Thr
                85                  90                  95

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

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
    210                 215


<210>  258
<211>  215
<212>  PRT
<213>  Homo Sapiens

<400>  258

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30
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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Arg
85 90 95

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala
100 105 110

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

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

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

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

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

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 259
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<213> Atificial

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<210> 260
<211> 23
<212> DNA
<213> Atificial

<400> 260

aagaccgatg ggcccttggt gga 23

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2005/000501

A. CLASSIFICATION OF SUBJECT MATTER
C07K16/34 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SHARON J ET AL: "CONSTRUCTION OF POLYCLONAL ANTIBODY LIBRARIES USING PHAGE DISPLAY" METHODS IN MOLECULAR BIOLOGY, HUMANA PRESS INC., CLIFTON, NJ, US, vol. 178, 2002, pages 101-112, XP008053600 the whole document	1-5, 9-11, 30-34, 41-45
Y	US 5 789 208 A (SHARON ET AL) 4 August 1998 (1998-08-04) cited in the application column 12, line 49 - line 65 column 14, line 25 - line 27 column 13, line 26 - line 34 column 14, line 17 - line 18	1-5, 9-11, 30-34, 41-45

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 November 2005	29/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Irion, A

INTERNATIONAL SEARCH REPORT

national application No.
PCT/DK2005/000501

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 51
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 51 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2005/000501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95/20401 A (TRUSTEES OF BOSTON UNIVERSITY) 3 August 1995 (1995-08-03) the whole document	1-5, 9-11, 30-34, 41-45
Y	BREGENHOLT S ET AL: "PATHOGEN-SPECIFIC RECOMBINANT HUMAN POLYCLONAL ANTIBODIES: BIODEFENCE APPLICATIONS" EXPERT OPINION ON BIOLOGICAL THERAPY, ASHLEY, LONDON, GB, vol. 4, no. 3, March 2004 (2004-03), pages 387-396, XP008030716 ISSN: 1471-2598 the whole document	1-5, 9-11, 30-34, 41-45
X	SELINGER M: "Immunoprophylaxis for rhesus disease--expensive but worth it?" BRITISH JOURNAL OF OBSTETRICS AND GYNAECOLOGY. JUN 1991, vol. 98, no. 6, June 1991 (1991-06), pages 509-512, XP009056635 ISSN: 0306-5456	46,48, 51-53
Y	the whole document	6-8, 35-40, 47,49,50
Y	WO 02/44361 A (APPLIED MOLECULAR EVOLUTION, INC; HUSE, WILLIAM, D) 6 June 2002 (2002-06-06) the whole document	1-5, 9-11, 30-34, 41-45
X	WO 97/49809 A (ROTKREUZSTIFTUNG ZENTRALLABORATORIUM BLUTSPENDEDIE; MIESCHER, SYLVIA;) 31 December 1997 (1997-12-31) cited in the application page 8, line 3 - line 5 page 9, line 15 - line 21 page 6, line 3 - line 5	12-15, 20,21, 26-29, 46,48, 51-53
Y		6-8, 35-40, 47,49,50
P,X	WO 2004/061104 A (SYMPHOGEN A/S; HAURUM, JOHN, S; WIBERG, FINN, C; COLJEE, VINCENT, W; S) 22 July 2004 (2004-07-22) the whole document	1-53

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2005/000501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	HAURUM JOHN ET AL: "Recombinant polyclonal antibodies: therapeutic antibody technologies come full circle." IDRUGS : THE INVESTIGATIONAL DRUGS JOURNAL. MAY 2005, vol. 8, no. 5, May 2005 (2005-05), pages 404-409, XP002352885 ISSN: 1369-7056 the whole document	1-53

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2005/000501

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5789208 A	04-08-1998	AT 300610 T	15-08-2005
		AT 243745 T	15-07-2003
		AU 1736495 A	15-08-1995
		DE 69531148 D1	31-07-2003
		DE 69531148 T2	29-04-2004
		DE 69534347 D1	01-09-2005
		DK 744958 T3	20-10-2003
		EP 0744958 A1	04-12-1996
		ES 2201097 T3	16-03-2004
		PT 744958 T	28-11-2003
		WO 9520401 A1	03-08-1995
WO 9520401 A	03-08-1995	AT 300610 T	15-08-2005
		AT 243745 T	15-07-2003
		AU 1736495 A	15-08-1995
		DE 69531148 D1	31-07-2003
		DE 69531148 T2	29-04-2004
		DE 69534347 D1	01-09-2005
		DK 744958 T3	20-10-2003
		EP 0744958 A1	04-12-1996
		ES 2201097 T3	16-03-2004
		PT 744958 T	28-11-2003
		US 5789208 A	04-08-1998
WO 0244361 A	06-06-2002	AU 3936902 A	11-06-2002
		CA 2430080 A1	06-06-2002
		EP 1337631 A2	27-08-2003
		JP 2004514444 T	20-05-2004
WO 9749809 A	31-12-1997	AT 272116 T	15-08-2004
		AU 722127 B2	20-07-2000
		AU 3342397 A	14-01-1998
		BG 64534 B1	30-06-2005
		BG 103016 A	31-08-1999
		BR 9709958 A	10-08-1999
		CA 2258494 A1	31-12-1997
		CZ 9803959 A3	12-05-1999
		DE 69730031 D1	02-09-2004
		DE 69730031 T2	16-06-2005
		ES 2224255 T3	01-03-2005
		HU 9902605 A2	29-11-1999
		JP 2000515732 T	28-11-2000
		KR 2000022530 A	25-04-2000
		NO 986088 A	24-02-1999
		NZ 333329 A	28-07-2000
		PL 330794 A1	07-06-1999
		RU 2204602 C2	20-05-2003
		SK 176198 A3	12-07-1999
		TR 9802692 T2	22-03-1999
WO 2004061104 A	22-07-2004	AU 2004203727 A1	22-07-2004
		EP 1583830 A2	12-10-2005