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(54) Title: HUMAN-ANTI-HUMAN CD3 BINDING MOLECULES

(57) Abstract: The present invention provides a method for the preparation of a human binding molecule, fragment or derivative thereof which specifically binds to the human CD3 complex. Furthermore, the invention provides a human binding molecules specifically binding to the human CD3 complex and means comprising said human binding molecules.

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Human anti-human CD3 Binding Molecules

The present invention relates to a method for the preparation of a human binding molecule, fragment or derivative thereof which specifically binds to the human CD3 complex. Furthermore, the invention relates to human binding molecules specifically binding to the human CD3 complex and means comprising said human binding molecules.

A variety of documents is cited throughout this specification. The disclosure content of said documents is herewith incorporated by reference.

Human CD3 antigen denotes an antigen which is expressed on T cells as part of the multimolecular T cell receptor complex (TCR) and which consists of three different chains: CD3-ε, CD3-δ and CD3-γ. Clustering of CD3 on T cells, e.g, by immobilized antibodies specific for the CD3 molecule leads to T cell activation similar to the engagement of the T cell receptor but independent of its clone-typical specificity. The individual proteins of the CD3 complex are referred to as δ, γ (both glycosylated) and ε (non-glycosylated). In the TCR/CD3 complex, CD3-ε exists as a dimer with either the CD3-δ or the CD3-γ signaling subunit. Upon dimerization with either the CD3-δ or the CD3-γ subunit, solely expressed, i.e. monomeric, CD3-ε undergoes a conformational change into its natural conformation (Kastrup, Scand. J. Immunol. 56 (2002), 436-42).

Owing to its central role in the modulation of T cell activity, the TCR/CD3 complex has been the subject of much research aimed at developing molecules capable of binding TCR/CD3. Much of this work has focused on the development of anti-TCR/CD3 monoclonal antibodies.

The prior art exemplifies antibodies with specificity for the human CD3 antigen. One such CD3 specific antibody is the murine monoclonal antibody OKT3 (proprietary name ORTHOCLONE®). OKT3 was the first monoclonal antibody drug approved by the FDA (approved in 1986). OKT3 has been described in the literature as a potent T cell mitogen (Van Wauve, J. Immunol. 124 (1980), 2708-18) as well as a potent T cell killer (Wong Transplantation 50 (1990), 683-9). OKT3 exhibits both of these activities in a time-dependent fashion; following early activation of T cells leading to cytokine release, upon further administration OKT3 later blocks all known T cell functions. It is due to this later blocking of T cell function that OKT3 has found such wide application as an immunosuppressant in therapy regimens for reduction or even abolition of allograft tissue rejection.

OKT3 reverses allograft tissue rejection most probably by blocking the function of all T cells which play a major role in acute rejection. OKT3 reacts with and blocks the function of the CD3 complex in the membrane of human T cells which is associated with the antigen recognition structure of T cells (TCR) and is essential for signal transduction. Which subunit of the TCR/CD3 is bound by OKT3 has been the subject of multiple studies. Though some evidence has pointed to a specificity of OKT3 for the ε-subunit of the TCR/CD3 complex (Tunnacliffe, Int. Immunol. 1 (1989), 546-50). Further evidence has shown that OKT3 binding of the TCR/CD3 complex requires other subunits of this complex to be present (Salmeron, J. Immunol. 147 (1991), 3047-52). The evidence relating to the exact epitope bound by OKT3 remains, then, ultimately inconclusive.

Patients treated with OKT3 experience a rapid and concomitant decrease in the number of circulating CD2+, CD3+, CD4+ and CD8+ cells within minutes following administration. This decrease in the number of CD3+ T cells results from the specific interaction between OKT3 and the CD3 surface antigen, ubiquitous on all T cells.

Other well known antibodies specific for the CD3 molecule are listed in Tunnacliffe,

Int. Immunol. 1 (1989), 546-50. As indicated above, such CD3 specific antibodies are able to induce various T cell responses such as lymphokine production (Von Wussow, J. Immunol. 127 (1981), 1197; Palacious, J. Immunol. 128 (1982), 337), proliferation (Van Wauve, J. Immunol. 124 (1980), 2708-18) and suppressor-T cell induction (Kunicka, in "Lymphocyte Typing II" 1 (1986), 223). That is, depending on the experimental conditions, CD3 specific monoclonal antibody can either inhibit or induce cytotoxicity (Leewenberg, J. Immunol. 134 (1985), 3770; Phillips, J. Immunol. 136 (1986) 1579; Platsoucas, Proc. Natl. Acad. Sci. USA 78 (1981), 4500; Itoh, Cell. Immunol. 108 (1987), 283-96; Mentzer, J. Immunol. 135 (1985), 34; Landegren, J. Exp. Med. 155 (1982), 1579; Choi (2001), Eur. J. Immunol. 31, 94-106; Xu (2000), Cell Immunol. 200, 16-26; Kimball (1995), Transpl. Immunol. 3, 212-221).

Another serious problem hampering the therapeutic use of, especially, murine monoclonal antibodies in humans is the mounting of a humoral immune response against such antibodies, resulting in the production of human anti-mouse antibodies ("HAMAs"). HAMAs are typically generated during the second week of treatment with the murine antibody and neutralize the murine antibodies, thereby blocking their ability to bind to their intended target. The HAMA response can depend on a number of factors, including the nature of the murine constant ("Fc") antibody regions, the nature of the murine variable ("V") regions, human Ig allotypes, unusual glycosylation of the murine antibody, the patient's MHC haplotype, the specificity of the murine antibody, whether the murine antibody binds to a surface antigen or a soluble antigen, whether the murine antibody forms immune complexes with the antigen, complement activation by the murine antibody, the ability of the murine antibody to bind the Fc receptor as well as the state of inflammation and/or cytokine release.

The prior art contains various approaches to reducing or preventing the production of HAMAs by modifying monoclonal antibodies.

One approach to reducing the immunogenicity of antibodies is by humanization, as for example described in WO 91/09968 and US 6,407,213. In general, humanization entails substitutions of non-human antibody sequences for corresponding human sequences, as for example is the case with CDR-grafting. In CDR-grafting, murine CDRs are inserted into human framework regions. However, being of murine origin, the grafted CDR regions can themselves lead to the production of HAMAs. Furthermore, CDR-grafting may affect the folding properties of the CDR regions, as the latter are at least partially dependent on amino acids in the original framework. Such alterations in the folding properties of the CDR regions can decrease the binding affinity and bioactivity of the CDR-grafted molecules. To ensure that the grafted CDR regions can fold into a conformation sufficient for the desired binding, certain murine amino acid residues considered important for the proper conformation of the amino acid residues within the CDR regions are reintroduced into the human framework region. However, such reintroduction can itself contribute to a production of HAMAs.

Another approach to reducing the immunogenicity of such antibodies is by deimmunization, as for example described in WO 92/10755, WO 00/34317, WO 98/52976, WO 02/079415, WO 02/012899 and WO 02/069232. In general, deimmunization entails carrying out substitutions of amino acids within potential T cell epitopes. In this way, the likelihood that a given sequence will give rise to T cell epitopes upon intracellular protein processing is reduced. However, deimmunization procedures such as those indicated above are purely predictive in nature, based as they are on theoretical approaches. For instance, predictions of potential T cell epitopes are made based on lists of known MHC haplotypes which are representative but incomplete. Therefore, it is impossible to ensure that removal of all predicted T cell epitopes will truly result in a fully deimmunized molecule.

Furthermore, both humanization and deimmunization approaches often lead to a significantly decreased binding affinity and therefore bioactivity with respect to the

non-modified species.

Despite the numerous disadvantages indicated above, recent literature indicates – in the specific context of CD3 specific antibodies – that humanization still represents the most feasible and promising mode of decreasing immunogenicity (Chatenoud, Nature Reviews 3 (2003), 123-32).

Thus, the technical problem underlying the present invention was to provide means and methods for binding molecules with specificity for the human CD3 complex which avoid the disadvantages of immunogenicity of molecules known in the art.

The solution to said technical problem is achieved by providing the embodiments characterized in the claims.

Accordingly, the present invention relates to a method for the preparation of a human binding molecule, fragment or derivative thereof which specifically binds to the human CD3 complex, said method comprising the steps of

(a) selecting molecules specifically binding to/interacting with the extracellular domain of the recombinant ε-chain, expressed independent of the human CD3 complex in the absence of other members of said CD3 complex, from a population of candidate polypeptides encoded by a library;

(b) selecting molecules from a population identified in step (a) for binding to the human CD3 complex; and

(c) preparation of said selected binding molecule.

The term "human binding molecule" defines a molecule of human source, i.e. of human origin. Said "human binding molecule" relates, for example, to (an) antibody molecule(s) or (a) fragment(s) thereof or to (a) specifically binding peptide(s) or protein(s) which is/are characterized by its/their ability to bind to the human CD3 complex, in particular to CD3 ε chain. As defined herein above, the CD3 complex is a part of the T-cell receptor (TCR).

The term "binding to/interacting with" as used in the context of the present invention defines a binding/interaction of at least two "antigen-interaction-sites" with each other. The term "antigen-interaction-site" defines, in accordance with the present invention, a motif of a polypeptide which is able to specifically interact with a specific antigen or a specific group of antigens. Said binding/interaction is also understood to define a "specific recognition". The term "specifically recognizing" means in accordance with this invention that the antibody molecule is capable of specifically interacting with and/or binding to at least two, preferably at least three, more preferably at least four amino acids of the human CD3 antigen as defined herein. Said term relates to the specificity of the antibody molecule, i.e. to its ability to discriminate between the specific regions of the human CD3 molecule as defined herein. The specific interaction of the antigen-interaction-site with its specific antigen may result in the initiation of a signal, e.g. due to the induction of a change of the conformation of the antigen, an oligomerization of the antigen, etc. Further, said binding may be exemplified by the specificity of a "lock-and-key-principle". Thus, specific motifs in the amino acid sequence of the antigen-interaction-site and the antigen bind to each other as a result of their primary, secondary or tertiary structure as well as the result of secondary modifications of said structure. The specific interaction of the antigen-interaction-site with its specific antigen may result as well in a simple binding of said site to the antigen.
The term "specific interaction" as used in accordance with the present invention means that the binding molecule does not or does not significantly cross-react with (poly)peptides which have similar structure as those bound by the binding molecule, and which are expressed by the same cells as the (poly)peptide of interest. Cross-reactivity of a panel of binding molecules under investigation may be tested, for example, by assessing binding of said panel of binding molecules under conventional conditions (see, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1988 and Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1999) .

Examples for the specific interaction of an antigen-interaction-site with a specific

antigen comprise the specificity of a ligand for its receptor. Said definition particularly comprises the interaction of ligands which induce a signal upon binding to its specific receptor. Examples for corresponding ligands comprise cytokines which interact/bind with/to their specific cytokine-receptors. Also particularly comprised by said definition is the binding of an antigen-interaction-site to antigens such as antigens of the selectin family, integrins and of the family of growth factors like EGF. Another example for said interaction, which is also particularly comprised by said definition, is the interaction of an antigenic determinant (epitope) with the antigenic binding site of an antibody.

The term "binding to/interacting with" may also relate to a conformational epitope, a structural epitope or a discontinuous epitope consisting of two regions of the human CD3 molecule or parts thereof. In the context of this invention, a conformational epitope is defined by two or more discrete amino acid sequences which are separated in the primary sequence, but which come together on the surface when the polypeptide folds to the native protein (Sela, (1969) Science 166, 1365 and Laver, (1990) Cell 61, 553-6).

The term "discontinuous epitope" means in context of the invention non-linear epitopes that are assembled from residues from distant portions of the polypeptide chain. These residues come together on the surface when the polypeptide chain folds into a three-dimensional structure to constitute a conformational/structural epitope.

The binding molecules of the present invention are also envisaged to specifically bind to/interact with a conformational/structural epitope(s) composed of and/or comprising at least two regions of the human CD3 complex, or composed of/comprising individual components, like CD3-ε, CD3-δ and CD3-γ and/or combinations of said components, such as CD3-ε/ CD3-δ or CD3-ε/ CD3-γ. Furthermore, it is envisaged that said conformational/structural epitope(s) described herein comprises individual parts/regions/stretches of at least two regions of a single component of the human CD3 complex, preferably at least two parts/regions/stretches of CD3-ε, even more preferably of the extracellular domain of CD3-ε.

Specificity of the human binding molecules obtained by the method of this invention can be determined experimentally by methods known in the art and methods as disclosed and described herein. Such methods comprise, but are not limited to Western blots, ELISA-, EIA-1, RIA-, ECL-, IRMA-tests and peptide scans.

According to the present invention "human binding molecules" are (poly)peptides which specifically bind to the human CD3 complex and/or its individual components. The term "(poly)peptide" as used herein describes a group of molecules which comprise the group of peptides, as well as the group of polypeptides. The group of peptides is consisting of molecules with up to 30 amino acids, the group of polypeptides is consisting of molecules with consisting of more than 30 amino acids. Most preferably, said "human binding molecules" are selected from the group of antibodies, antibody fragments, antibody derivatives, specific binding peptides and specific binding proteins. Said antibody fragments are known in the art and comprise, but are not limited to, Fab-fragments, $F(ab_2)'$ fragments, Fv fragments and the like. As will be detailed below, particular preferred fragments of antibodies in context of this invention are scFv fragments. Antibody derivatives comprise but are not limited to labeled antibodies/antibody fragments as well as chemically modified antibody molecules/antibody fragments. Therefore, fragments or derivatives of the recited human binding molecules also relate to (poly)peptides which are parts of the above defined (poly)peptides or which are modified posttranslationally or by chemical/biochemical or molecular biological methods. Corresponding methods are known in the art and are described, inter alia, in laboratory manuals (see Sambrook et al.; Molecular Cloning: A Laboratory Manual; Cold Spring Harbor Laboratory Press, 2nd edition 1989 and 3rd edition 2001; Gerhardt et al.; Methods for General and Molecular Bacteriology; ASM Press, 1994; Lefkovits; Immunology Methods Manual: The Comprehensive Sourcebook of Techniques; Academic Press, 1997; Golemis; Protein-Protein Interactions: A Molecular Cloning Manual; Cold Spring Harbor Laboratory Press, 2002).

The recited extracellular domain of the recombinant ε-chain of the CD3 complex is known in the art and relates, in accordance with this invention, to the term "extracellular domain of recombinant ε-chain" and/or to the term "extracellular domain of human CD3-ε". Said extracellular domain comprises the amino acid positions 23 to 126 of the known human CD3-ε, as documented in NM_000733 / NP_000724 Homo sapiens CD3E [gi:4502670 / gi:450267]. In accordance with the present invention, a particular preferred extracellular domain of human CD3-ε is encoded by a nucleic acid molecule as shown in SEQ ID NO. 140. It is also envisaged that only parts of the extracellular domain of human CD3 ε-chain are employed in the method of the present invention. Yet, it is to be understood that the method of the present invention may also be carried out with recombinantly expressed extracellular domains of CD3 ε-chain which are homologous or mutated in relation to the extracellular domain shown in SEQ ID NO: 141. For example, the method of the present invention may be carried out with recombinantly expressed extracellular domains of CD3 ε-chains which are genetic variants, for example allelic variants, of the extracellular domain of the human CD3 ε chain. Such variants also comprise CD3 ε-chains from closely related primates. Preferably, said primate CD3 ε-chains, respectively their extracellular domains shown an homology to the human CD3 ε-chain of at least 80%, more preferably of at least 90%, most preferably of at least 95%.

For the step of selection of binding molecules of the present inventive method, said ε-chain is expressed independent of the human CD3 complex in the absence of other members of said CD3 complex. In the absence of other members of the complex the ε-chain is folded without any support in its folding by said other members. Consequently, the antigenicity of some domains of the ε-chain is different from the antigenicity of said other domains when the ε-chain is expressed in the context of the CD3 complex. The cloning and expression of the CD3 ε-chain is exemplified in the appended Example 1.

The selection recited in steps (a) and (b) of the method of the invention particularly

comprises the selection of binding molecules by affinity selection. Methods for affinity selection are known in the art (see Golemis, loc cit.; Rehm, Der Experimentator: Proteinbiochemie/Proteomics, Spektrum Akademischer Verlag, 2002; Lottspeich and Zorbas, Bioanalytik, Spektrum Akademischer Verlag, 1998). One embodiment of a corresponding method is described in appended Example 2.

The term "population of candidate polypeptides" defines the population of polypeptides from which the binding molecules are selected from. In accordance with the present invention said polypeptides are encoded by a library. Thus, said population may be a peptide library as well as a population of peptides encoded by a library. Examples for said libraries comprise DNA-libraries such as cDNA-libraries and RNA-libraries, see, inter alia, Hoogenboom (2000) Immun Today 21, 371-378. The preparation of a cDNA-library is exemplified in the appended examples.

One population of candidate polypeptides is described in the appended examples as peptides encoded by a library derived from human cells, wherein the genes of said library encode human antibody molecules. Human antibody molecules encoded by said genes with specificity for the human CD3 complex are not expressed by mature B cells in the human body. This is because of the above discussed lack of T helper cell signals for self-reactive B cells (specific for autoantigens) since the necessary self-reactive T helper cells have been eliminated during the intrathymic clonal deletion of self-reactive pre-T cells.

Identification of autoantigen-specific human antibodies from a library derived from such human B cells is therefore highly unlikely. When considering the human CD3 antigen, ubiquitously expressed throughout the entire T cell compartment, this likelihood is decreased even further. Human B cells which, by chance or accident, produce and surface-display an Ig with specificity for human CD3, and which by binding of the human CD3 antigen activate $CD8^+$ T cells, will be killed by the very $CD8^+$ cells they themselves activate (Itoh, Cellular Immunol. 108 (1987) 313-22; Hoffman, J. Immunol. 135 (1985), 5-8). The subpopulation of B cells bearing anti-human CD3 specific antibodies on their surface therefore becomes depleted below its already naturally low level within the entire B cell compartment. A random cross-

section of B cells from the B cell compartment, such as is used in constructing a diverse antibody library, is thus all the less likely to comprise B cells producing antibody specific for human CD3. This explains the difficulty in identifying antibodies of human origin against the autoantigen human CD3 using antibody library techniques.

Said obstacle has been surprisingly overcome by the present invention which resulted in the preparation of binding molecules with specificity for the human CD3 complex, wherein said binding molecules themselves are human derived/of human origin. Due to the human source of the binding molecule, said molecules are most preferably non-immunogenic (or at least minimally immunogenic) for the human immune system under physiological conditions.

The term "preparation" as used in the present specification and in particular in the above described inventive method, defines method steps such as recovery of a peptide from a binding partner, i.e. from the ε-chain of the human CD3 complex, the purification of said peptide as well as their corresponding isolation, their further determination (like sequencing), the isolation/generation of corresponding encoding nucleic acid molecules as well as their expansion (general reproduction, recombinant reproduction, chemical synthesis, in-vitro translation etc). Corresponding techniques are detailed below and also shown in the appended examples.

A particularly surprising advantage of the present invention is the provision of human binders (in particular antibody binders) against the human CD3 antigen, which overcome several major limitations in the field of antibody technology.

In general, it is known that developing B cells which exhibit a binding specificity for autoantigens are naturally selected against before the mature B cells are released into the bloodstream. As such, human B cells in the blood which produce monoclonal antibody against human antigen make up an exceedingly small proportion of the peripheral B cell compartment. Identification of autoantigen-specific human antibodies from an antibody library derived from such human B

cells is therefore highly unlikely. When considering the human CD3 antigen, ubiquitously expressed throughout the entire T cell compartment, this likelihood is decreased even further. Human B cells which, by chance or accident, produce and surface-display an Ig with specificity for human CD3, and which by binding of the human CD3 antigen activate CD8+ T cells, will be killed by the very CD8+ cells they themselves activate (i.e. redirected lysis) (Itoh, Cellular Immunol. 108 (1987) 313-22; Hoffman, J. Immunol. 135 (1985), 5-8). The subpopulation of B cells bearing anti-human CD3 antibodies on their surface therefore becomes depleted below its already naturally low level within the entire B cell compartment. A random cross-section of B cells from the B cell compartment, such as is used in constructing a diverse antibody library, is thus all the less likely to comprise B cells producing antibody specific for human CD3. This explains the difficulty in identifying antibodies of human origin against the autoantigen human CD3 using antibody library techniques.

The above mentioned hurdles are surprisingly overcome by the method of the present invention, in particular by using an appropriate protein for selection of antibodies from a library, in particular from an antibody library. In accordance with this invention, solely expressed recombinant CD3-epsilon protein is used for selection of a CD3 binder, in particular an antibody binder from a diverse library, e.g. an antibody library derived from human B cells. Without being bound by theory, it is believed that the conformation adopted by solely expressed recombinant CD3-epsilon protein differs from that adopted in its natural form, that is, the form in which the CD3-epsilon subunit of the TCR/CD3 complex exists as part of a noncovalent complex with either the CD3-delta or the CD3-gamma subunit of the TCR/CD3 complex (Kastrup, Scand. J. Immunol. 56 (2002) 436-42). Were natural CD3-epsilon in its complexed form to be used as an antigen for selection of antibodies from an antibody library, the probability of identifying an antibody specifically binding to this protein would be very low. This is because the cells generating antibodies with binding specificity for natural CD3-epsilon are preferentially depleted in vivo from the compartment used to construct the antibody

library. However, when solely expressed recombinant CD3-epsilon protein is used as an antigen for selection of antibodies from an antibody library, antibodies specific for this antigen are identified from the library. This is due to the fact that solely expressed recombinant CD3-epsilon protein does not exist in vivo; it is not an autoantigen. Consequently, subpopulations of B cells expressing antibodies specific for this protein have not been depleted in vivo; an antibody library constructed from such B cells would contain genetic material for antibodies specific for solely expressed recombinant CD3-epsilon protein.

A major advantage according to the invention is that binders, like antibodies identified from (antibody) libraries as specific binders of solely expressed recombinant CD3-epsilon are also able to specifically bind CD3-epsilon in its natural, complexed form. This is especially surprising, given the failure of natural, complexed CD3-epsilon to identify specific antibodies when this protein is used as the selection antigen for human antibody libraries. According to the invention, the recombinant form of CD3-epsilon thus acts as a surrogate antigen which can be used to identify human antibodies to the human CD3 antigen. Such antibodies would normally remain unidentifiable using naturally-expressed human CD3 antigen in its complexed form.

In a further embodiment, the invention relates to the above described method, further comprising a step (d), relating to the identification of the nucleic acid sequence encoding the human CD3 binding molecule in the library.

As mentioned above, said identification may comprise the sequence-analysis of the amino acid sequence of the selected polypeptide or the sequence-analysis of the nucleic acid molecule coding for the selected polypeptide. Methods for said analysis are known in the art. Furthermore, examples for said identification are described in the appended examples 2.8 and 3.2.

In accordance with the present invention, the recited library which encodes the candidate polypeptides may be derived from a DNA-library or an RNA-library. Particularly comprised by said definition are cDNA-libraries.

Further in accordance with the invention the library which encodes the candidate polypeptides is derived from primary or secondary lymphatic organs of humans. Said sources particularly comprise fetuses. Examples for said lymphatic organs are spleen, lymph nodes, MALT (mucosa associated lymphatic tissues), bone marrow, blood, proliferative disorder tissue, tonsil, umbilical cord blood and inflammatory tissue.

As pointed out above, in the method of the invention said selection of the human binding molecules may be effected by exposing the human binding molecules to immobilized recombinant, solely expressed ε- chain, expressed independent of the human CD3 complex in the absence of other members of said CD3 complex. The recombinant ε- chain may be immobilized or adsorbed on a solid support/surface. Examples for said solid support/surface are known in the art and comprise, inter alia, polymeric surfaces, such as polystyrene, polypropylene as well as specifically coated surfaces like PolySorp™, MaxiSorp™, MultiSorp™, etc.

According to a preferred embodiment of the method of the invention, the selection step of the method of the invention comprises a phage display method. Phage display technology has been described in the literature, for example in Hoogenboom, Methods Mol Biol 178 (2002), 1-37, Pini, Curr Protein Prep Sci 1 (2000), 155-69. A description of the selection of phage-displayed antibodies is described e.g. in Mutuberria, J. Immunol. Methods 231 (1999), 65-81. Phage display methology is also described in WO 99/25818 and is also exemplified in the appended examples.

As mentioned above and illustrated in the appended examples, the human binding molecule, fragment or derivative thereof, which is prepared/isolated by the method of the invention is preferably an antibody molecule, antibody fragment or derivative thereof or a construct comprising at least one antibody, antibody fragment or derivative thereof which specifically binds to the human CD3 complex.

Said antibody is preferably a monoclonal antibody. The term "antibody fragment or derivative thereof" relates to single chain antibodies, or fragment thereof, synthetic antibodies, antibody fragments, such as Fab, a $F(ab_2)'$, Fv or scFv fragments etc., or a chemically modified derivative of any of these. Antibodies to be employed in accordance with the invention or their corresponding immunoglobulin chain(s) can be further modified using conventional techniques known in the art, for example, by using amino acid deletion(s), insertion(s), substitution(s), addition(s), and/or recombination(s) and/or any other modification(s) known in the art either alone or in combination. Methods for introducing such modifications in the DNA sequence underlying the amino acid sequence of an immunoglobulin chain are well known to the person skilled in the art; see, e.g., Sambrook (1989), loc. cit.

According to a further preferred embodiment of the method of the invention, said method for the production of human anti-human CD3 binding molecules further comprises the steps of:

I: (a) taking the VH and/or VL region/s of at least one of the isolated human CD3 binders and (i) inserting mutations resulting in amino acid substitutions (e.g. as described in Barbas III, TIBTECH 14 (1996) 230, Schier, J. Mol. Biol. 263 (1996) 551, Hawkins, J. Mol. Biol. 226 (1992) 889) and/or (ii) shuffling a repertoire of human V-regions to the VH or VL of said human CD3 binders (e.g. as described in Raum, Cancer Immunol Immunother 50 (2001) 141-150) and/or

(b) grafting at least one CDR of at least one of the isolated human CD3 binders into the corresponding position/s of the variable regions of a human antibody library (e.g. principle of inserting predetermined CDR/s into the context of human antibody libraries e.g. as described in Rader, PNAS 95 (1998) 8910-5, Steinberger, J Biol Chem 17 (2000) 36073-8)

and

II: subjecting the resulting library/ies to further selection on human CD3 antigen or parts thereof (e.g. for the purpose of affinity maturation). The CD3 antigen or parts thereof used for selection may be expressed (naturally or via transfection)

on cells (e.g. T cells, see Tunnacliffe, International Immunology 1 (1989) 546) or isolated from a natural source (e.g. immunoprecipitated from human T cells following the method as described e.g. by Leo, PNAS 84 (1997) 1374-1378 adapted to human CD3) or produced as recombinant protein (as described e.g. in the present invention or by Tunnacliffe, Immunol. Lett. 21 (1989) 243, Kastrup, Scand. J. Immunol. 56 (2002) 436-442), Kim, J. Mol. Biol. 302 (2000) 899-916 adapted to human CD3) or synthesized as peptide.

The term "antibody fragment or derivative thereof" particularly relates to (poly)peptide constructs comprising at least one CDR

The complementary determining region (CDR) dictates the antigen specificity of the response and plays a central role in initiating activation. However, this interaction, by itself, is not sufficient to fully activate naïve T cells. After the initial T cell stimulation there have to be further, antigen-independent co-stimulatory signals.

It is particularly envisaged by the invention that said derivative of an antibody is an scFv. The term "scFv fragment" (single-chain Fv fragment) is well understood in the art. ScFvs are preferred in context of this invention, due to their small size and the possibility of recombinantly producing these antibody fragments.

According to a preferred embodiment of the invention said human binding molecule specifically binding to the human CD3 complex is an antibody molecule, antibody fragment, derivative thereof or antibody construct comprising at least one further antigen-interaction-site and/or at least one further effector domain.

Examples for the recited "further effector domain" comprise signal inducing domains of molecules, wherein the initiation of said signal results in the uptake of the molecule into the cell, cell death, cell proliferation or cell stimulation. Examples of such effector domains comprise, but are not limited to, B7.1, Fas-ligand, cytokines (like IL2), NKG-2D, NKD-46, OX40L or 4.1BBL. Corresponding binding molecules comprise bispecific constructs in molecular format as described e.g. in WO 99/54440 as well as molecular formats as described in WO 00/06605.

Preferably said bispecific constructs are bispecific single chain antibody construct. The term "single-chain" as used in accordance with the present invention means that said first and second domain of the bispecific single chain construct are covalently linked, preferably in the form of a co-linear amino acid sequence encodable by a single nucleic acid molecule.

Preferably it is envisaged that said antibody molecule, antibody fragment, derivative thereof or construct is humanized and/or deimmunized in an additional step.

Since the domain specifically binding to/interacting with the human CD3 complex is a human (poly)peptide or human (poly)peptide fragment it is envisaged that only parts of said at least one further antigen-interaction-site and/or at least one further effector domain which are non-human derived are humanized. The non-human derived domains of said antibody molecule, antibody fragment, derivative thereof or construct may be also or alternatively be deimmunized. Furthermore, the fusion of human derived domains to non-human derived domains, preferably by the linker referred above, may result in immunogenic epitopes. Corresponding epitopes at said junctions between human derived domains and non-human derived domains may also be deleted by deimmunization. Methods for the humanization of antibodies and antibody constructs are known in the art and described e.g. in EP-A1 0 239 400, WO 90/07861, Welt (2003) Clin Cancer Res 9, 1338-1346. Methods for the deimunization of (poly)peptides and (poly)peptide constructs are known in the art and described e.g. in WO 02/079415, WO02/069232 or WO00/34317.

Further in accordance with the invention said further antigen-interaction-site of the human binding molecule specific for human CD3 complex and as described herein is, in addition, specific for one or more cell surface molecule.

The term "cell surface molecule" as used herein denotes molecules which are presented or/and attached on/to the surface of a cell. Examples for said cell surface molecules are membrane and transmembrane proteins (including modified

variants, such as glycosylated variants), molecules attached to said proteins or the cell surface as well as glycosylated moieties such as for example lipids. Attachment is to be understood as being effected by way of an integral membrane protein, a GPI-linked (glycosyl phosphatidyl inositol-linked) protein, a proteinaceous or non-proteinaceous moiety bound covalently or non-covalently to another carrier molecule such as sugar moieties or ganglioside moieties. Preferably said cell surface molecule is a tumor-specific marker. A tumor-specific marker is a tumor-associated cell surface antigen which is either found exclusively on tumor cells or is overexpressed on tumor cells as compared to non-malignant cells. Tumor-associated cell surface antigens can be expressed not only on tumor cells but also on cells/tissue which are/is not essential for survival or which can be replenished by stem cells not expressing tumor-associated cell surface antigen. Furthermore, tumor-associated cell surface antigen can be expressed on malignant cells and non-malignant cells but is better accessible by a therapeutic agent of interest on malignant cells. Examples of over-expressed tumor-associated cell surface antigens are Her2/neu, EGF-Receptor, Her-3 and Her-4. An example of a tumor-associated cell surface antigen which is tumor specific is EGFRV-III. An example of a tumor-associated cell surface antigen which is presented on a cell which is non-essential for survival is PSMA. Examples of tumor-associated cell surface antigens which are presented on cells which are replenished are CD19, CD20 and CD33. An example of a tumor-associated cell surface antigen which is better accessible in a malignant state than in a non-malignant state is EpCAM.

It is envisaged and documented herein that said at least one further antigen-interaction-site is a domain which is derived from an antibody or antibody construct.

Preferably, said domain which is an antibody-derived region comprises a polypeptide sequence which corresponds to at least one variable region of an antibody. More preferably, said at least one further antigen-interaction-site is a further scFv. A particularly preferred molecular format of the invention provides a

polypeptide construct wherein the antibody-derived region comprises one V_H and one V_L region.

The term "bispecific single chain antibody construct" relates to a construct comprising one domain consisting of (at least one) variable region(s) (or parts thereof) as defined above capable of specifically interacting with/binding to human CD3/human CD3 complex and comprising a second domain consisting of (at least one) variable region(s) (or parts thereof) as defined above capable of specifically interacting with/binding to a further antigen.

Said binding/interaction is also understood to define a "specific recognition". The term "specifically recognizing" means in accordance with this invention that the antibody molecule is capable of specifically interacting with and/or binding to at least two amino acids of each of the human target molecule as defined herein. Said term relates to the specificity of the antibody molecule, i.e. to its ability to discriminate between the specific regions of the human target molecule as defined herein. The specific interaction of the antigen-interaction-site with its specific antigen may result in an initiation of a signal, e.g. due to the induction of a change of the conformation of the antigen, an oligomerization of the antigen, etc. Further, said binding may be exemplified by the specificity of a "key-lock-principle". Thus, specific motifs in the amino acid sequence of the antigen-interaction-site and the antigen bind to each other as a result of their primary, secondary or tertiary structure as well as the result of secondary modifications of said structure. The specific interaction of the antigen-interaction-site with its specific antigen may result as well in a simple binding of said site to the antigen.

The term "specific interaction" as used in accordance with the present invention means that the bispecific single chain construct does not or essentially does not cross-react with (poly)peptides of similar structures. Cross-reactivity of a panel of bispecific single chain construct under investigation may be tested, for example, by assessing binding of said panel of bispecific single chain construct under conventional conditions (see, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1988 and Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, 1999) to the

(poly)peptide of interest as well as to a number of more or less (structurally and/or functionally) closely related (poly)peptides. Only those antibodies that bind to the (poly)peptide/protein of interest but do not or do not essentially bind to any of the other (poly)peptides are considered specific for the (poly)peptide/protein of interest. Examples for the specific interaction of an antigen-interaction-site with a specific antigen comprise the specificity of a ligand for its receptor. Said definition particularly comprises the interaction of ligands which induce a signal upon binding to its specific receptor. Examples for corresponding ligands comprise cytokines which interact/bind with/to its specific cytokine-receptors. Also particularly comprised by said definition is the binding of an antigen-interaction-site to antigens like antigens of the selectin family, integrins and of the family of growth factors like EGF. An other example for said interaction, which is also particularly comprised by said definition, is the interaction of an antigenic determinant (epitope) with the antigenic binding site of an antibody.

The term "binding to/interacting with" may also relate to a conformational epitope, a structural epitope or a discountinuous epitope consisting of two regions of the human target molecules or parts thereof. In context of this invention, a conformational epitope is defined by two or more discrete amino acid sequences separated in the primary sequence which come together on the surface of the molecule when the polypeptide folds to the native protein (Sela, (1969) Science 166, 1365 and Laver, (1990) Cell 61, 553-6).

The term "discontinuous epitope" means in context of the invention non-linear epitopes that are assembled from residues from distant portions of the polypeptide chain. These residues come together on the surface of the molecule when the polypeptide chain folds into a three-dimensional structure to constitute a conformational/structural epitope.

According to the present invention the term "variable region" used in the context with Ig-derived antigen-interaction comprises fragments and derivatives of (poly)peptides which at least comprise one CDR derived from an antibody, antibody fragment or derivative thereof. It is envisaged by the invention, that said at least one CDR is preferably a CDR3, more preferably the CDR3 of the heavy chain

of an antibody (CDR-H3). However, other antibody derived CDRs are also particularly comprised by the term "variable region"

The "specific binding" of an antibody is characterized primarily by two parameters: a qualitative parameter (the binding epitope, or *where* the antibody binds) and a quantitative parameter (the binding affinity, or *how strongly* it binds where it does). Which epitope is bound by an antibody can advantageously be determined by e.g. known FACS methodology, peptide-spot epitope mapping, mass spectroscopy. The strength of antibody binding to a particular epitope may be advantageously be determined by e.g. known BIAcore and/or ELISA methodologies. A combination of such techniques allows the calculation of a signal:noise ratio as a representative measure of binding specificity. In such a signal:noise ratio, the signal represents the strength of antibody binding to the epitope of interest, whereas the noise represents the strength of antibody binding to other, non-related epitopes differing from the epitope of interest. In general, any time an antibody binds more frequently and/or strongly to one epitope than another epitope, such antibody may be said to bind the former epitope specifically. Preferably, a signal:noise ratio for an epitope of interest which is about 50-fold higher than for other epitopes different from the epitope of interest may be taken as an indication that the antibody evaluated binds the epitope of interest in a specific manner, i.e. is a "specific binder".

A part of a variable region may be at least one CDR ("Complementary Determining Region"), most preferably at least the CDR3 region. Said two domains/regions in the single chain antibody construct are preferably covalently connected to one another as a single chain. This connection can be effected either directly (domain1 interacting with CD3 – domain2 interacting with the further antigen or domain1 interacting with the further antigen – domain2 interacting with CD3) or through an additional polypeptide linker sequence (domain1 – linker sequence – domain2 or domain2 – linker sequence – domain1). In the event that a linker is used, this linker is preferably of a length and sequence sufficient to ensure that each of the first and second domains can, independently from one another, retain their differential binding specificities. Most preferably and as documented in the appended examples, the "bispecific single chain antibody construct" is a bispecific single

chain Fv (bscFv). Bispecific single chain molecules are known in the art and are described in WO 99/54440, Mack, J. Immunol. (1997), 158, 3965-3970, Mack, PNAS, (1995), 92, 7021-7025; Kufer, Cancer Immunol. Immunother., (1997), 45, 193-197;Löffler, Blood, (2000), 95, 6, 2098-2103; Brühl, Immunol., (2001), 166, 2420-2426. Distinct examples for such bispecific single chain antibody construct are provided herein below and illustrated in the appended examples.

In accordance with the invention, said at least one further antigen-interaction-site specifically binds to/interacts with an antigen selected from the group consisting of EpCAM, CCR5, CD19, EphA2, HER-2 neu, HER-3, HER-4, EGFR, PSMA, CEA, MUC-1 (mucin), MUC2, MUC3, MUC4, $MUC5_{AC}$, $MUC5_{B}$, MUC7, βhCG, Lewis-Y, CD20, CD22, CD52, CD33, CD30, ganglioside GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, Carboanhydrase IX (MN/CA IX), CD44v6, Sonic Hedgehog (Shh), Wue-1, Plasma Cell Antigen, (membrane-bound) IgE, Melanoma Chondroitin Sulfate Proteoglycan (MCSP), CCR8, TNF-alpha precursor, STEAP, STEAP II, mesothelin, A33 Antigen, Prostate Stem Cell Antigen (PSCA), Ly-6; desmoglein 4, E-cadherin neoepitope, Fetal Acetylcholine Receptor, CD25, CA19-9 marker, CA-125 marker and Muellerian Inhibitory Substance (MIS) Receptor type II, sTn (sialylated Tn antigen; TAG-72), FAP (fibroblast activation antigen), endosialin, EGFRvIII, L6, SAS , CD63, Tu, TF, Le^a, Sialyl Le^a, Le^b, Le^x, Sialyl Le^x and polyfucosyl-Le^x.

Optionally the method of the invention may further comprise the step of recombinant expression of the binding molecule, fragment or derivative thereof encoded by a nucleic acid sequence selected from the group consisting of:

(a) the identified nucleic acid sequence;

(b) a nucleic acid sequence hybridizing with the complementary strand of the identified nucleic acid sequence under stringent hybridization conditions;

(c) a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (a) and (b).

The term "hybridizing" as used herein refers to polynucleotides which are capable of hybridizing to the recited nucleic acid sequence or parts thereof. Therefore, said

nucleic acid sequence may be useful as probes in Northern or Southern Blot analysis of RNA or DNA preparations, respectively, or can be used as oligonucleotide primers in PCR analysis dependent on their respective size. Preferably, said hybridizing polynucleotides comprise at least 10, more preferably at least 15 nucleotides while a hybridizing polynucleotide of the present invention to be used as a probe preferably comprises at least 100, more preferably at least 200, or most preferably at least 500 nucleotides.

It is well known in the art how to perform hybridization experiments with nucleic acid molecules, i.e. the person skilled in the art knows what hybridization conditions s/he has to use in accordance with the present invention. Such hybridization conditions are referred to in standard text books such as Sambrook et al. (loc cit.) and other standard laboratory manuals known by the person skilled in the art or as recited above. Preferred in accordance with the present inventions are polynucleotides which are capable of hybridizing to the polynucleotides of the invention or parts thereof, under stringent hybridization conditions.

"Stringent hybridization conditions" refer, i.e. to an overnight incubation at 42°C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1 x SSC at about 65°C. Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1 X SSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC). It is of note that variations in the above conditions may be accomplished

through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

The recited nucleic acid molecules may be, e.g., DNA, cDNA, RNA or synthetically produced DNA or RNA or a recombinantly produced chimeric nucleic acid molecule comprising any of those polynucleotides either alone or in combination.

The invention further relates to a method, wherein said optional step of recombinant expression of the binding molecule, fragment or derivative thereof encoded by a nucleic acid sequence comprises the preparation of a vector comprising said nucleic acid sequence.

Many suitable vectors are known to those skilled in molecular biology, the choice of which would depend on the function desired and would include plasmids, cosmids, viruses, bacteriophages and other vectors used conventionally in genetic engineering. Methods which are well known to those skilled in the art can be used to construct various plasmids and vectors; see, for example, the techniques described in Sambrook et al. (loc cit.) and Ausubel, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N.Y. (1989), (1994). Alternatively, the polynucleotides and vectors of the invention can be reconstituted into liposomes for delivery to target cells. As discussed in further details below, a cloning vector was used to isolate individual sequences of DNA. Relevant sequences can be transferred into expression vectors where expression of a particular polypeptide is required. Typical cloning vectors include pBluescript SK, pGEM, pUC9, pBR322 and pGBT9. Typical expression vectors include pTRE, pCAL-n-EK, pESP-1, pOP13CAT.

Also in accordance with the invention said vector further comprises a nucleic acid

sequence which is a regulatory sequence operably linked to said identified nucleic acid sequence.

The term " regulatory sequence" refers to DNA sequences which are necessary to effect the expression of coding sequences to which they are ligated. The nature of such control sequences differs depending upon the host organism. In prokaryotes, control sequences generally include promoter, ribosomal binding site, and terminators. In eukaryotes control sequences generally include promoters, terminators and, in some instances, enhancers, transactivators or transcription factors. The term "control sequence" is intended to include, at a minimum, all components the presence of which are necessary for expression, and may also include additional advantageous components.

The term "operably linked" refers to a arrangement/configuration wherein the components so described are in a relationship permitting them to function in their intended manner. A control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences. In case the control sequence is a promoter, it is obvious for a skilled person that double-stranded nucleic acid is preferably used.

Thus, the recited vector is preferably an expression vector. An "expression vector" is a construct that can be used to transform a selected host and provides for expression of a coding sequence in the selected host. Expression vectors can for instance be cloning vectors, binary vectors or integrating vectors. Expression comprises transcription of the nucleic acid molecule preferably into a translatable mRNA. Regulatory elements ensuring expression in prokaryotes and/or eukaryotic cells are well known to those skilled in the art. In the case of eukaryotic cells they comprise normally promoters ensuring initiation of transcription and optionally poly-A signals ensuring termination of transcription and stabilization of the transcript. Possible regulatory elements permitting expression in prokaryotic hosts comprise, e.g., the P_L, *lac*, *trp* or *tac* promoter in *E. coli*, and examples of regulatory elements permitting expression in eukaryotic host cells are the *AOX1* or *GAL1* promoter in yeast or the CMV-, SV40-, RSV-promoter (Rous sarcoma virus), CMV-enhancer,

SV40-enhancer or a globin intron in mammalian and other animal cells.

Besides elements which are responsible for the initiation of transcription such regulatory elements may also comprise transcription termination signals, such as the SV40-poly-A site or the tk-poly-A site, downstream of the polynucleotide. Furthermore, depending on the expression system used, leader sequences capable of directing the polypeptide to a cellular compartment or secreting it into the medium may be added to the coding sequence of the recited nucleic acid sequence and are well known in the art; see also, e.g., the appended examples. The leader sequence(s) is (are) assembled in appropriate phase with translation, initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein, or a portion thereof, into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product; see supra. In this context, suitable expression vectors are known in the art such as Okayama-Berg cDNA expression vector pcDV1 (Pharmacia), pCDM8, pRc/CMV, pcDNA1, pcDNA3 (In-vitrogene), pEF-DHFR and pEF-ADA (Raum et al. Cancer Immunol Immunother (2001) 50(3), 141-150) or pSPORT1 (GIBCO BRL).

Preferably, the expression control sequences will be eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells, but control sequences for prokaryotic hosts may also be used. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences, and as desired, the collection and purification of the polypeptide of the invention may follow; see, e.g., the appended examples.

An alternative expression system which could be used to express a cell cycle interacting protein is an insect system. In one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. The coding sequence of a recited nucleic acid molecule may be cloned into a nonessential region of the virus,

such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of said coding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein coat. The recombinant viruses are then used to infect *S. frugiperda* cells or *Trichoplusia* larvae in which the protein of the invention is expressed (Smith, J. Virol. 46 (1983), 584; Engelhard, Proc. Nat. Acad. Sci. USA 91 (1994), 3224-3227).

Additional regulatory elements may include transcriptional as well as translational enhancers. Advantageously, the above-described vectors of the invention comprises a selectable and/or scorable marker.

Selectable marker genes useful for the selection of transformed cells and, e.g., plant tissue and plants are well known to those skilled in the art and comprise, for example, antimetabolite resistance as the basis of selection for dhfr, which confers resistance to methotrexate (Reiss, Plant Physiol. (Life Sci. Adv.) 13 (1994), 143-149); npt, which confers resistance to the aminoglycosides neomycin, kanamycin and paromycin (Herrera-Estrella, EMBO J. 2 (1983), 987-995) and hygro, which confers resistance to hygromycin (Marsh, Gene 32 (1984), 481-485). Additional selectable genes have been described, namely trpB, which allows cells to utilize indole in place of tryptophan; hisD, which allows cells to utilize histinol in place of histidine (Hartman, Proc. Natl. Acad. Sci. USA 85 (1988), 8047); mannose-6-phosphate isomerase which allows cells to utilize mannose (WO 94/20627) and ODC (ornithine decarboxylase) which confers resistance to the ornithine decarboxylase inhibitor, 2-(difluoromethyl)-DL-ornithine, DFMO (McConlogue, 1987, In: Current Communications in Molecular Biology, Cold Spring Harbor Laboratory ed.) or deaminase from Aspergillus terreus which confers resistance to Blasticidin S (Tamura, Biosci. Biotechnol. Biochem. 59 (1995), 2336-2338).

Useful scorable marker are also known to those skilled in the art and are commercially available. Advantageously, said marker is a gene encoding luciferase (Giacomin, Pl. Sci. 116 (1996), 59-72; Scikantha, J. Bact. 178 (1996), 121), green fluorescent protein (Gerdes, FEBS Lett. 389 (1996), 44-47) or ß-glucuronidase (Jefferson, EMBO J. 6 (1987), 3901-3907). This embodiment is particularly useful for simple and rapid screening of cells, tissues and organisms containing a recited

vector.

As described above, the recited nucleic acid molecule can be used alone or as part of a vector to express the encoded polypeptide in cells, for, e.g., gene therapy. The nucleic acid molecules or vectors containing the DNA sequence(s) encoding any one of the above described human binding molecules is introduced into the cells which in turn produce the polypeptide of interest. Gene therapy, which is based on introducing therapeutic genes into cells by ex-vivo or in-vivo techniques is one of the most important applications of gene transfer. Suitable vectors, methods or gene-delivery systems for in-vitro or in-vivo gene therapy are described in the literature and are known to the person skilled in the art; see, e.g., Giordano, Nature Medicine 2 (1996), 534-539; Schaper, Circ. Res. 79 (1996), 911-919; Anderson, Science 256 (1992), 808-813; Verma, Nature 389 (1994), 239; Isner, Lancet 348 (1996), 370-374; Muhlhauser, Circ. Res. 77 (1995), 1077-1086; Onodera, Blood 91 (1998), 30-36; Verma, Gene Ther. 5 (1998), 692-699; Nabel, Ann. N.Y. Acad. Sci. 811 (1997), 289-292; Verzeletti, Hum. Gene Ther. 9 (1998), 2243-51; Wang, Nature Medicine 2 (1996), 714-716; WO 94/29469; WO 97/00957, US 5,580,859; US 5,589,466; or Schaper, Current Opinion in Biotechnology 7 (1996), 635-640. The recited nucleic acid molecules and vectors may be designed for direct introduction or for introduction via liposomes, or viral vectors (e.g., adenoviral, retroviral) into the cell. Preferably, said cell is a germ line cell, embryonic cell, or egg cell or derived therefrom, most preferably said cell is a stem cell. An example for an embryonic stem cell can be, inter alia, a stem cell as described in, Nagy, Proc. Natl. Acad. Sci. USA 90 (1993), 8424-8428.

In accordance with the above, the present invention relates to method to derive vectors, particularly plasmids, cosmids, viruses and bacteriophages used conventionally in genetic engineering that comprise a nucleic acid molecule encoding the polypeptide sequence of a human binding molecule. Preferably, said vector is an expression vector and/or a gene transfer or targeting vector. Expression vectors derived from viruses such as retroviruses, vaccinia virus, adeno-associated virus, herpes viruses, or bovine papilloma virus, may be used for

delivery of the recited polynucleotides or vector into targeted cell populations. Methods which are well known to those skilled in the art can be used to construct recombinant vectors; see, for example, the techniques described in Sambrook et al. (loc cit.), Ausubel (1989, loc cit.) or other standard text books. Alternatively, the recited nucleic acid molecules and vectors can be reconstituted into liposomes for delivery to target cells. The vectors containing the nucleic acid molecules of the invention can be transferred into the host cell by well-known methods, which vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotes, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts; see Sambrook, supra. The recited vector may be the pEF-Neo, pEF-DHFR or pEF-ADA. The vectors pEF-DHFR and pEF-ADA have been described in the art, e.g. in Mack, PNAS (1995) 92, 7021-7025 and Raum, Cancer Immunol Immunother (2001) 50(3), 141-150.
It is further envisaged that the method of the invention further comprises the step of transforming a host with the above described vector.

Said host may be produced by introducing said at least one of the above described vector or at least one of the above described nucleic acid molecules into the host. The presence of said at least one vector or at least one nucleic acid molecule in the host may mediate the expression of a gene encoding the above described human binding molecule. The described nucleic acid molecule or vector which is introduced in the host may either integrate into the genome of the host or it may be maintained extrachromosomally.

The host can be any prokaryotes or eukaryotic cell.

The term "prokaryote" is meant to include all bacteria which can be transformed or transfected with a DNA or RNA molecules for the expression of a protein of the invention. Prokaryotic hosts may include gram negative as well as gram positive bacteria such as, for example, E. coli, S. typhimurium, Serratia marcescens and Bacillus subtilis. The term "eukaryotic" is meant to include yeast, higher plant,

insect and preferably mammalian cells. Depending upon the host employed in a recombinant production procedure, the protein encoded by the polynucleotide of the present invention may be glycosylated or may be non-glycosylated. Especially preferred is the use of a plasmid or a virus containing the coding sequence of the polypeptide of the invention and genetically fused thereto an N-terminal FLAG-tag and/or C-terminal His-tag. Preferably, the length of said FLAG-tag is about 4 to 8 amino acids, most preferably 8 amino acids. An above described polynucleotide can be used to transform or transfect the host using any of the techniques commonly known to those of ordinary skill in the art. Furthermore, methods for preparing fused, operably linked genes and expressing them in, e.g., mammalian cells and bacteria are well-known in the art (Sambrook, loc cit.).

Preferably, said host is a bacteria, an insect, fungal, plant or animal cell. It is particularly envisaged that the recited host may be a mammalian cell, more preferably a human cell or human cell line. Particularly preferred host cells comprise CHO cells, COS cells, myeloma cell lines like SP2/0 or NS/0.

It is further envisaged that the method of the invention may comprise the step of isolation and/or purification of the recombinantly expressed human binding molecule, fragment or derivative thereof. Said method consequently comprises the step of culturing a recited host under conditions allowing the expression of the recited human binding molecule and recovering said binding molecule from the culture. The transformed hosts can be grown in fermentors and cultured according to techniques known in the art to achieve optimal cell growth. The human binding molecule can then be isolated from the culture medium, cellular lysates, or cellular membrane fractions. The isolation and purification of the, say, microbially expressed human binding molecules may be effected by any conventional means such as, for example, preparative chromatographic separations and immunological separations such as those involving the use of monoclonal or polyclonal antibodies directed, for example against a tag of the human binding molecule or as described in the appended examples.

The conditions for the culturing of a host which allow the expression are known in the art to depend on the host system and the expression system/vector used in such process. The parameters to be modified in order to achieve conditions allowing the expression of a recombinant polypeptide are known in the art. Thus, suitable conditions can be determined by the person skilled in the art in the absence of further inventive input.

Once expressed, the human binding molecule can be purified according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, column chromatography, gel electrophoresis and the like; see, Scopes, "Protein Purification", Springer-Verlag, N.Y. (1982). Substantially pure polypeptides of at least about 90 to 95% homogeneity are preferred, and 98 to 99% or more homogeneity are most preferred, for pharmaceutical uses. Once purified, partially or to homogeneity as desired, the human binding molecules may then be used therapeutically (including extracorporeally) or in developing and performing assay procedures. Furthermore, examples for methods for the recovery human binding molecules from a culture are described in detail in the appended examples.

In a preferred embodiment of the method of the invention, said method further comprises the step of formulating the human binding molecule as a pharmaceutical composition, which optionally further comprises a pharmaceutically acceptable carrier or diluent.

The term "pharmaceutical composition" as well as the terms "pharmaceutically acceptable carrier" and "pharmaceutically acceptable diluent" are defined in more detail herein below.

In an alternative embodiment the present invention relates to a human binding molecule specifically binding to/interacting with the human CD3 complex, whereby said binding molecule is an antibody molecule, antibody fragment or derivative thereof or an antibody construct.

As described herein above, the method of the invention provides means for the preparation/isolation of a human binding molecule of the invention. Said particular human binding molecule of the invention is an antibody molecule, antibody fragment or derivative thereof or an antibody construct.

The terms "antibody molecule", "antibody fragment or derivative thereof" and "antibody construct" have been defined in the context of the above described method of the invention. In line with said definitions the antibody fragment or derivative thereof or an antibody construct of the invention comprises at least one CDR of a human antibody with specificity for the human CD3 complex, preferably at least one CDR3, which provides the capacity of the binding molecule to bind to/interact with the human CD3 complex.

The human binding molecule of the invention may comprise an additional domain which may be used for the isolation/preparation of the molecule. Examples for said additional domain comprise label and tags. Said tag may be selected from the group consisting of: His-tag, Flag-tag, Myc-tag, HA-tag, GST-tag, T100™, VSV-G, V5, S-tag™, HSV, CFP, RFP, YFP, GFP, BFP, Cellulose binding domain (CBD), Maltose binding protein (MBP), NusA-tag, thioredoxin (Trx), DsbA, DabC and a biotinylation sequence.

A human binding molecule wherein said derivative of an antibody is an scFv is particularly envisaged by the present invention.

As also discussed herein above, the terms "antibody fragment or derivative thereof" and "antibody construct" relate, inter alia, to scFv constructs. The intramolecular orientation of the V_H-domain and the V_L-domain, which are linked to each other by a linker-domain, in the scFv format is not decisive for binding molecules of the invention. Thus, scFvs with both possible arrangements (V_H-domain – linker domain – V_L-domain; V_L-domain – linker domain – V_H-domain) are particular embodiments of the human binding molecule of the invention.

A corresponding format of the human binding molecule of the invention is described in the appended example 3.2.

A human binding molecule of the invention is characterized as an antibody molecule, antibody fragment or derivative thereof or an antibody construct, which comprises a variable V_H-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 1,17, 33, 49, 65, 81, 97 and 113 or a variable V_H-region having an amino acid sequence as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98 and 114.

Alternatively, the human binding molecule of the invention is characterized as an antibody molecule, antibody fragment or derivative thereof or an antibody construct, which comprises a variable V_L-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105 and 121 or a variable V_L-region having an amino acid sequence as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106 and 122.

The human binding molecule of the invention may also comprise at least one CDR3 of a V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 7, 23, 39, 55, 71, 87, 103 or 119 or at least one CDR3 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104 or 120 and/or wherein said antibody molecule comprises at least one CDR3 of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 15, 31, 47, 63, 79, 95, 111 or 127 or at least one CDR3 amino acid sequence of a V_L-region as shown in SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112 or 128.

Alternatively the human binding molecule of the invention may also comprise at least one CDR2 of an V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 5, 21, 37, 53, 69, 85, 101 or 117 or at least one CDR2 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102 or 118 and/or wherein said antibody molecule comprises at least one CDR2 of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 13, 29,

45, 61, 77, 93, 109 or 125 or at least one CDR2 amino acid sequence of an V_L-region as shown in SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110 or 126.

A further alternative human binding molecule of the invention is characterized as an antibody molecule, antibody fragment or derivative thereof or an antibody construct, which comprises at least one CDR1 of an V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 3, 19, 35, 51, 67, 83, 99 or 115 or at least one CDR1 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100 or 116 and/or wherein said antibody molecule comprises at least one CDR1 of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 11, 27, 43, 59, 75, 91, 107 or 123 or at least one CDR1 amino acid sequence of an V_L-region as shown in SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108 or 124.

It is further envisaged by the present invention that the human binding molecule additionally comprises at least one further antigen-interaction-site and/or at least one further effector domain.

The invention also relates to multispecific binding molecules. Bi-, tri-, tetra- as well as oligo-specific binding molecule are particularly comprised. The term "further effector domain" has been defined and exemplified herein above.

Human binding molecules of the invention, which comprise at least one further antigen-interaction-site and/or at least one further effector domain, may be humanized and/or deimmunized.

As noted herein above only non-human derived domains of the binding molecule may be humanized. Furthermore, immunogenic epitopes, at the junctions between human derived domains and non-human derived domains and in non-human derived domains may be deleted by deimmunization. Methods for the humanization and or deimmunization of corresponding domains are known by the person skilled

in the art and some possible methods have been discussed herein above.

In one embodiment of the human binding molecule of the invention, said at least one further antigen-interaction-site is specific for one or more cell surface molecule.

The terms "cell surface molecule" and "tumor marker/tumor specific marker" have been defined herein above. Preferably said cell surface molecule is a tumor specific marker. Examples for said tumor specific markers are TAG72, PSMA, CD44v6, CEA, Her2-neu, Her-3, Her-4, Lewis Y. Further markers have been described above.

It is also envisaged that said at least one further antigen-interaction-site is a domain which is derived from an antibody or antibody construct.

Preferably, said domain which is an antibody-derived region comprises a polypeptide sequence which corresponds to at least one variable region of an antibody. More preferably, said at least one further antigen-interaction-site is a further scFv. A particularly preferred molecular format of the invention provides a polypeptide construct wherein the antibody-derived region comprises one V_H and one V_L region.

The intramolecular orientation (N-terminal or C-terminal) of the different antigen interaction-sites (domains) in the human binding molecule is not decisive for the invention as long as said different antigen interaction-sites specifically bind to/interact with its specific antigens. Consequently, in the case of a bispecific binding molecule the domain specific for the human CD3 complex may be N-terminal (and the further antigen-interaction-site C-terminal) as well as C-terminal (and the further antigen-interaction-site N-terminal).

Preferably said at least one further antigen-interaction-site is a further scFv. In the particular format of an scFv the orientation of the V_H-domain and the V_L-domain in the domain of the further antigen-interaction-site is not decisive for the present

invention. Thus, scFvs with both possible arrangements in the portion of the further antigen-interaction-site (V_H-domain – linker domain – V_L-domain; V_L-domain – linker domain – V_H-domain) are particular embodiments of the human binding molecule of the invention. Accordingly, for a corresponding bispecific human binding molecule said permutation of domains results in eight possible constructs for one specific human binding molecule.

In accordance with the invention said at least one further antigen-interaction-site specifically binds to/interacts with an antigen selected from the group consisting of EpCAM, CCR5, CD19, EphA2, HER-2 neu, HER-3, HER-4, EGFR, PSMA, CEA, TAG-72, MUC-1 (mucin), MUC2, MUC3, MUC4, $MUC5_{AC}$, $MUC5_B$, MUC7, βhCG, Lewis-Y, CD20, CD33, CD30, ganglioside GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, Carboanhydrase IX (MN/CA IX), CD44v6, Sonic Hedgehog (Shh), Wue-1, Plasma Cell Antigen, (membrane-bound) IgE, Melanoma Chondroitin Sulfate Proteoglycan (MCSP), CCR8, TNF-alpha precursor, STEAP, STEAP II, mesothelin, A33 Antigen, Prostate Stem Cell Antigen (PSCA), Ly-6, desmoglein 4, E-cadherin neoepitope, Fetal Acetylcholine Receptor, CD25, CA19-9 marker, CA-125 marker and Muellerian Inhibitory Substance (MIS) Receptor type II, sTn (sialylated Tn antigen; TAG-72), FAP (fibroblast activation antigen), endosialin, EGFRvIII, L6, SAS , CD63, Tu, TF, Le^a, Sialyl Le^a, Le^b, Le^x, Sialyl Le^x and polyfucosyl-Le^x.

In the following tables 1 to 8, specific bispecific constructs comprising as one specificity the human anti-human CD3 binder as described herein are provided. The following tables 1 and 2 relate to the above described embodiment of the present invention and describe specific human anti-human CD3xCD19 constructs. The following tables 3 and 4 relate to the above described embodiment of the present invention and describe specific human anti-human CD3xEpCAM constructs. The following tables 5 and 6 relate to the above described embodiment of the present invention and describe specific human anti-human CD3xCCR5 constructs. The following tables 7 and 8 relate to the above-described embodiment

of the present invention and describe specific human anti-human CD3xCD20 constructs. In this context, it is of note that tables 1, 3, 5 and 7 relate to nucleic acid sequences encoding the corresponding bispecific constructs, whereas tables 2, 4, 6 and 8, respectively, show the corresponding proteinaceous sequences.

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The following tables 1,3, 5 and 7 depict selected nucleic acid molecules encoding specific constructs of the inventions.

Table 1:

Construct	SEQ ID NO in construct portion ...							h anti-hCD3 construct / Specificity (N -> C) / Domain Arrangement
	A	B	C	D	E	F	G	
1nuc	9	174	1	176	129	174	131	3-106 / CD3xCD19 / LHHL
2nuc	1	174	9	176	129	174	131	3-106 / CD3xCD19 / HLHL
3nuc	9	174	1	176	131	174	129	3-106 / CD3xCD19 / LHLH
4nuc	1	174	9	176	131	174	129	3-106 / CD3xCD19 / HLLH
5nuc	131	174	129	176	1	174	9	3-106 / CD19xCD3 / LHHL
6nuc	129	174	131	176	1	174	9	3-106 / CD19xCD3 / HLHL
7nuc	131	174	129	176	9	174	1	3-106 / CD19xCD3 / LHLH
8nuc	129	174	131	176	9	174	1	3-106 / CD19xCD3 / HLLH
9nuc	25	174	17	176	129	174	131	3-114 / CD3xCD19 / LHHL
10nuc	17	174	25	176	129	174	131	3-114 / CD3xCD19 / HLHL
11nuc	25	174	17	176	131	174	129	3-114 / CD3xCD19 / LHLH
12nuc	17	174	25	176	131	174	129	3-114 / CD3xCD19 / HLLH
13nuc	131	174	129	176	17	174	25	3-114 / CD19xCD3 / LHHL
14nuc	129	174	131	176	17	174	25	3-114 / CD19xCD3 / HLHL
15nuc	131	174	129	176	25	174	17	3-114 / CD19xCD3 / LHLH
16nuc	129	174	131	176	25	174	17	3-114 / CD19xCD3 / HLLH
17nuc	41	174	33	176	129	174	131	3-148 / CD3xCD19 / LHHL
18nuc	33	174	41	176	129	174	131	3-148 / CD3xCD19 / HLHL
19nuc	41	174	33	176	131	174	129	3-148 / CD3xCD19 / LHLH
20nuc	33	174	41	176	131	174	129	3-148 / CD3xCD19 / HLLH
21nuc	131	174	129	176	33	174	41	3-148 / CD19xCD3 / LHHL
22nuc	129	174	131	176	33	174	41	3-148 / CD19xCD3 / HLHL
23nuc	131	174	129	176	41	174	33	3-148 / CD19xCD3 / LHLH
24nuc	129	174	131	176	41	174	33	3-148 / CD19xCD3 / HLLH
25nuc	57	174	49	176	129	174	131	3-190 / CD3xCD19 / LHHL

26nuc	49	174	57	176	129	174	131	3-190 / CD3xCD19 / HLHL
27nuc	57	174	49	176	131	174	129	3-190 / CD3xCD19 / LHLH
28nuc	49	174	57	176	131	174	129	3-190 / CD3xCD19 / HLLH
29nuc	131	174	129	176	49	174	57	3-190 / CD19xCD3 / LHHL
30nuc	129	174	131	176	49	174	57	3-190 / CD19xCD3 / HLHL
31nuc	131	174	129	176	57	174	49	3-190 / CD19xCD3 / LHLH
32nuc	129	174	131	176	57	174	49	3-190 / CD19xCD3 / HLLH
33nuc	73	174	65	176	129	174	131	3-271 / CD3xCD19 / LHHL
34nuc	65	174	73	176	129	174	131	3-271 / CD3xCD19 / HLHL
35nuc	73	174	65	176	131	174	129	3-271 / CD3xCD19 / LHLH
36nuc	65	174	73	176	131	174	129	3-271 / CD3xCD19 / HLLH
37nuc	131	174	129	176	65	174	73	3-271 / CD19xCD3 / LHHL
38nuc	129	174	131	176	65	174	73	3-271 / CD19xCD3 / HLHL
39nuc	131	174	129	176	73	174	65	3-271 / CD19xCD3 / LHLH
40nuc	129	174	131	176	73	174	65	3-271 / CD19xCD3 / HLLH
41nuc	89	174	81	176	129	174	131	3-550 / CD3xCD19 / LHHL
42nuc	81	174	89	176	129	174	131	3-550 / CD3xCD19 / HLHL
43nuc	89	174	81	176	131	174	129	3-550 / CD3xCD19 / LHLH
44nuc	81	174	89	176	131	174	129	3-550 / CD3xCD19 / HLLH
45nuc	131	174	129	176	81	174	89	3-550 / CD19xCD3 / LHHL
46nuc	129	174	131	176	81	174	89	3-550 / CD19xCD3 / HLHL
47nuc	131	174	129	176	89	174	81	3-550 / CD19xCD3 / LHLH
48nuc	129	174	131	176	89	174	81	3-550 / CD19xCD3 / HLLH
49nuc	105	174	97	176	129	174	131	4-10 / CD3xCD19 / LHHL
50nuc	97	174	105	176	129	174	131	4-10 / CD3xCD19 / HLHL
51nuc	105	174	97	176	131	174	129	4-10 / CD3xCD19 / LHLH
52nuc	97	174	105	176	131	174	129	4-10 / CD3xCD19 / HLLH
53nuc	131	174	129	176	97	174	105	4-10 / CD19xCD3 / LHHL
54nuc	129	174	131	176	97	174	105	4-10 / CD19xCD3 / HLHL
55nuc	131	174	129	176	105	174	97	4-10 / CD19xCD3 / LHLH

56nuc	129	174	131	176	105	174	97	4-10 / CD19xCD3 / HLLH
57nuc	121	174	113	176	129	174	131	4-48 / CD3xCD19 / LHHL
58nuc	113	174	121	176	129	174	131	4-48 / CD3xCD19 / HLHL
59nuc	121	174	113	176	131	174	129	4-48 / CD3xCD19 / LHLH
60nuc	113	174	121	176	131	174	129	4-48 / CD3xCD19 / HLLH
61nuc	131	174	129	176	113	174	121	4-48 / CD19xCD3 / LHHL
62nuc	129	174	131	176	113	174	121	4-48 / CD19xCD3 / HLHL
63nuc	131	174	129	176	121	174	113	4-48 / CD19xCD3 / LHLH
64nuc	129	174	131	176	121	174	113	4-48 / CD19xCD3 / HLLH

Table 3:

Construct	SEQ ID NO in construct portion ...							h anti-hCD3 construct / Specificity (N -> C) / Domain Arrangement
	A	B	C	D	E	F	G	
65nuc	9	174	1	176	133	174	135	3-106 / CD3xEpCAM / LHHL
66nuc	1	174	9	176	133	174	135	3-106 / CD3xEpCAM / HLHL
67nuc	9	174	1	176	135	174	133	3-106 / CD3xEpCAM / LHLH
68nuc	1	174	9	176	135	174	133	3-106 / CD3xEpCAM / HLLH
69nuc	135	174	133	176	1	174	9	3-106 / EpCAMxCD3 / LHHL
70nuc	133	174	135	176	1	174	9	3-106 / EpCAMxCD3 / HLHL
71nuc	135	174	133	176	9	174	1	3-106 / EpCAMxCD3 / LHLH
72nuc	133	174	135	176	9	174	1	3-106 / EpCAMxCD3 / HLLH
73nuc	25	174	17	176	133	174	135	3-114 / CD3xEpCAM / LHHL
74nuc	17	174	25	176	133	174	135	3-114 / CD3xEpCAM / HLHL
75nuc	25	174	17	176	135	174	133	3-114 / CD3xEpCAM / LHLH
76nuc	17	174	25	176	135	174	133	3-114 / CD3xEpCAM / HLLH
77nuc	135	174	133	176	17	174	25	3-114 / EpCAMxCD3 / LHHL
78nuc	133	174	135	176	17	174	25	3-114 / EpCAMxCD3 / HLHL
79nuc	135	174	133	176	25	174	17	3-114 / EpCAMxCD3 / LHLH

80nuc	133	174	135	176	25	174	17	3-114 / EpCAMxCD3 / HLLH
81nuc	41	174	33	176	133	174	135	3-148 / CD3xEpCAM / LHHL
82nuc	33	174	41	176	133	174	135	3-148 / CD3xEpCAM / HLHL
83nuc	41	174	33	176	135	174	133	3-148 / CD3xEpCAM / LHLH
84nuc	33	174	41	176	135	174	133	3-148 / CD3xEpCAM / HLLH
85nuc	135	174	133	176	33	174	41	3-148 / EpCAMxCD3 / LHHL
86nuc	133	174	135	176	33	174	41	3-148 / EpCAMxCD3 / HLHL
87nuc	135	174	133	176	41	174	33	3-148 / EpCAMxCD3 / LHLH
88nuc	133	174	135	176	41	174	33	3-148 / EpCAMxCD3 / HLLH
89nuc	57	174	49	176	133	174	135	3-190 / CD3xEpCAM / LHHL
90nuc	49	174	57	176	133	174	135	3-190 / CD3xEpCAM / HLHL
91nuc	57	174	49	176	135	174	133	3-190 / CD3xEpCAM / LHLH
92nuc	49	174	57	176	135	174	133	3-190 / CD3xEpCAM / HLLH
93nuc	135	174	133	176	49	174	57	3-190 / EpCAMxCD3 / LHHL
94nuc	133	174	135	176	49	174	57	3-190 / EpCAMxCD3 / HLHL
95nuc	135	174	133	176	57	174	49	3-190 / EpCAMxCD3 / LHLH
96nuc	133	174	135	176	57	174	49	3-190 / EpCAMxCD3 / HLLH
97nuc	73	174	65	176	133	174	135	3-271 / CD3xEpCAM / LHHL
98nuc	65	174	73	176	133	174	135	3-271 / CD3xEpCAM / HLHL
99nuc	73	174	65	176	135	174	133	3-271 / CD3xEpCAM / LHLH
100nuc	65	174	73	176	135	174	133	3-271 / CD3xEpCAM / HLLH
101nuc	135	174	133	176	65	174	73	3-271 / EpCAMxCD3 / LHHL
102nuc	133	174	135	176	65	174	73	3-271 / EpCAMxCD3 / HLHL
103nuc	135	174	133	176	73	174	65	3-271 / EpCAMxCD3 / LHLH
104nuc	133	174	135	176	73	174	65	3-271 / EpCAMxCD3 / HLLH
105nuc	89	174	81	176	133	174	135	3-550 / CD3xEpCAM / LHHL
106nuc	81	174	89	176	133	174	135	3-550 / CD3xEpCAM / HLHL
107nuc	89	174	81	176	135	174	133	3-550 / CD3xEpCAM / LHLH
108nuc	81	174	89	176	135	174	133	3-550 / CD3xEpCAM / HLLH
109nuc	135	174	133	176	81	174	89	3-550 / EpCAMxCD3 / LHHL

110nuc	133	174	135	176	81	174	89	3-550 / EpCAMxCD3 / HLHL
111nuc	135	174	133	176	89	174	81	3-550 / EpCAMxCD3 / LHLH
112nuc	133	174	135	176	89	174	81	3-550 / EpCAMxCD3 / HLLH
113nuc	105	174	97	176	133	174	135	4-10 / CD3xEpCAM / LHHL
114nuc	97	174	105	176	133	174	135	4-10 / CD3xEpCAM / HLHL
115nuc	105	174	97	176	135	174	133	4-10 / CD3xEpCAM / LHLH
116nuc	97	174	105	176	135	174	133	4-10 / CD3xEpCAM / HLLH
117nuc	135	174	133	176	97	174	105	4-10 / EpCAMxCD3 / LHHL
118nuc	133	174	135	176	97	174	105	4-10 / EpCAMxCD3 / HLHL
119nuc	135	174	133	176	105	174	97	4-10 / EpCAMxCD3 / LHLH
120nuc	133	174	135	176	105	174	97	4-10 / EpCAMxCD3 / HLLH
121nuc	121	174	113	176	133	174	135	4-48 / CD3xEpCAM / LHHL
122nuc	113	174	121	176	133	174	135	4-48 / CD3xEpCAM / HLHL
123nuc	121	174	113	176	135	174	133	4-48 / CD3xEpCAM / LHLH
124nuc	113	174	121	176	135	174	133	4-48 / CD3xEpCAM / HLLH
125nuc	135	174	133	176	113	174	121	4-48 / EpCAMxCD3 / LHHL
126nuc	133	174	135	176	113	174	121	4-48 / EpCAMxCD3 / HLHL
127nuc	135	174	133	176	121	174	113	4-48 / EpCAMxCD3 / LHLH
128nuc	133	174	135	176	121	174	113	4-48 / EpCAMxCD3 / HLLH

Table 5:

Construct	SEQ ID NO in construct portion ...							h anti-hCD3 construct / Specificity (N -> C) / Domain Arrangement
	A	B	C	D	E	F	G	
129nuc	9	174	1	176	196	174	198	3-106 / CD3xCCR5 / LHHL
130nuc	1	174	9	176	196	174	198	3-106 / CD3xCCR5 / HLHL
131nuc	9	174	1	176	198	174	196	3-106 / CD3xCCR5 / LHLH
132nuc	1	174	9	176	198	174	196	3-106 / CD3xCCR5 / HLLH
133nuc	198	174	196	176	1	174	9	3-106 / CCR5xCD3 / LHHL

134nuc	196	174	198	176	1	174	9	3-106 / CCR5xCD3 / HLHL
135nuc	198	174	196	176	9	174	1	3-106 / CCR5xCD3 / LHLH
136nuc	196	174	198	176	9	174	1	3-106 / CCR5xCD3 / HLLH
137nuc	25	174	17	176	196	174	198	3-114 / CD3xCCR5 / LHHL
138nuc	17	174	25	176	196	174	198	3-114 / CD3xCCR5 / HLHL
139nuc	25	174	17	176	198	174	196	3-114 / CD3xCCR5 / LHLH
140nuc	17	174	25	176	198	174	196	3-114 / CD3xCCR5 / HLLH
141nuc	198	174	196	176	17	174	25	3-114 / CCR5xCD3 / LHHL
142nuc	196	174	198	176	17	174	25	3-114 / CCR5xCD3 / HLHL
143nuc	198	174	196	176	25	174	17	3-114 / CCR5xCD3 / LHLH
144nuc	196	174	198	176	25	174	17	3-114 / CCR5xCD3 / HLLH
145nuc	41	174	33	176	196	174	198	3-148 / CD3xCCR5 / LHHL
146nuc	33	174	41	176	196	174	198	3-148 / CD3xCCR5 / HLHL
147nuc	41	174	33	176	198	174	196	3-148 / CD3xCCR5 / LHLH
148nuc	33	174	41	176	198	174	196	3-148 / CD3xCCR5 / HLLH
149nuc	198	174	196	176	33	174	41	3-148 / CCR5xCD3 / LHHL
150nuc	196	174	198	176	33	174	41	3-148 / CCR5xCD3 / HLHL
151nuc	198	174	196	176	41	174	33	3-148 / CCR5xCD3 / LHLH
152nuc	196	174	198	176	41	174	33	3-148 / CCR5xCD3 / HLLH
153nuc	57	174	49	176	196	174	198	3-190 / CD3xCCR5 / LHHL
154nuc	49	174	57	176	196	174	198	3-190 / CD3xCCR5 / HLHL
155nuc	57	174	49	176	198	174	196	3-190 / CD3xCCR5 / LHLH
156nuc	49	174	57	176	198	174	196	3-190 / CD3xCCR5 / HLLH
157nuc	198	174	196	176	49	174	57	3-190 / CCR5xCD3 / LHHL
158nuc	196	174	198	176	49	174	57	3-190 / CCR5xCD3 / HLHL
159nuc	198	174	196	176	57	174	49	3-190 / CCR5xCD3 / LHLH
160nuc	196	174	198	176	57	174	49	3-190 / CCR5xCD3 / HLLH
161nuc	73	174	65	176	196	174	198	3-271 / CD3xCCR5 / LHHL
162nuc	65	174	73	176	196	174	198	3-271 / CD3xCCR5 / HLHL
163nuc	73	174	65	176	198	174	196	3-271 / CD3xCCR5 / LHLH

164nuc	65	174	73	176	198	174	196	3-271 / CD3xCCR5 / HLLH
165nuc	198	174	196	176	65	174	73	3-271 / CCR5xCD3 / LHHL
166nuc	196	174	198	176	65	174	73	3-271 / CCR5xCD3 / HLHL
167nuc	198	174	196	176	73	174	65	3-271 / CCR5xCD3 / LHLH
168nuc	196	174	198	176	73	174	65	3-271 / CCR5xCD3 / HLLH
169nuc	89	174	81	176	196	174	198	3-550 / CD3xCCR5 / LHHL
170nuc	81	174	89	176	196	174	198	3-550 / CD3xCCR5 / HLHL
171nuc	89	174	81	176	198	174	196	3-550 / CD3xCCR5 / LHLH
172nuc	81	174	89	176	198	174	196	3-550 / CD3xCCR5 / HLLH
173nuc	198	174	196	176	81	174	89	3-550 / CCR5xCD3 / LHHL
174nuc	196	174	198	176	81	174	89	3-550 / CCR5xCD3 / HLHL
175nuc	198	174	196	176	89	174	81	3-550 / CCR5xCD3 / LHLH
176nuc	196	174	198	176	89	174	81	3-550 / CCR5xCD3 / HLLH
177nuc	105	174	97	176	196	174	198	4-10 / CD3xCCR5 / LHHL
178nuc	97	174	105	176	196	174	198	4-10 / CD3xCCR5 / HLHL
179nuc	105	174	97	176	198	174	196	4-10 / CD3xCCR5 / LHLH
180nuc	97	174	105	176	198	174	196	4-10 / CD3xCCR5 / HLLH
181nuc	198	174	196	176	97	174	105	4-10 / CCR5xCD3 / LHHL
182nuc	196	174	198	176	97	174	105	4-10 / CCR5xCD3 / HLHL
183nuc	198	174	196	176	105	174	97	4-10 / CCR5xCD3 / LHLH
184nuc	196	174	198	176	105	174	97	4-10 / CCR5xCD3 / HLLH
185nuc	121	174	113	176	196	174	198	4-48 / CD3xCCR5 / LHHL
186nuc	113	174	121	176	196	174	198	4-48 / CD3xCCR5 / HLHL
187nuc	121	174	113	176	198	174	196	4-48 / CD3xCCR5 / LHLH
188nuc	113	174	121	176	198	174	196	4-48 / CD3xCCR5 / HLLH
189nuc	198	174	196	176	113	174	121	4-48 / CCR5xCD3 / LHHL
190nuc	196	174	198	176	113	174	121	4-48 / CCR5xCD3 / HLHL
191nuc	198	174	196	176	121	174	113	4-48 / CCR5xCD3 / LHLH
192nuc	196	174	198	176	121	174	113	4-48 / CCR5xCD3 / HLLH

Table 7:

Construct	SEQ ID NO in construct portion ...							h anti-hCD3 construct / Specificity (N -> C) / Domain Arrangement
	A	B	C	D	E	F	G	
193nuc	9	174	1	176	200	174	202	3-106 / CD3xCD20 / LHHL
194nuc	1	174	9	176	200	174	202	3-106 / CD3xCD20 / HLHL
195nuc	9	174	1	176	202	174	200	3-106 / CD3xCD20 / LHLH
196nuc	1	174	9	176	202	174	200	3-106 / CD3xCD20 / HLLH
197nuc	202	174	200	176	1	174	9	3-106 / CD20xCD3 / LHHL
198nuc	200	174	202	176	1	174	9	3-106 / CD20xCD3 / HLHL
199nuc	202	174	200	176	9	174	1	3-106 / CD20xCD3 / LHLH
200nuc	200	174	202	176	9	174	1	3-106 / CD20xCD3 / HLLH
201nuc	25	174	17	176	200	174	202	3-114 / CD3xCD20 / LHHL
202nuc	17	174	25	176	200	174	202	3-114 / CD3xCD20 / HLHL
203nuc	25	174	17	176	202	174	200	3-114 / CD3xCD20 / LHLH
204nuc	17	174	25	176	202	174	200	3-114 / CD3xCD20 / HLLH
205nuc	202	174	200	176	17	174	25	3-114 / CD20xCD3 / LHHL
206nuc	200	174	202	176	17	174	25	3-114 / CD20xCD3 / HLHL
207nuc	202	174	200	176	25	174	17	3-114 / CD20xCD3 / LHLH
208nuc	200	174	202	176	25	174	17	3-114 / CD20xCD3 / HLLH
209nuc	41	174	33	176	200	174	202	3-148 / CD3xCD20 / LHHL
210nuc	33	174	41	176	200	174	202	3-148 / CD3xCD20 / HLHL
211nuc	41	174	33	176	202	174	200	3-148 / CD3xCD20 / LHLH
212nuc	33	174	41	176	202	174	200	3-148 / CD3xCD20 / HLLH
213nuc	202	174	200	176	33	174	41	3-148 / CD20xCD3 / LHHL
214nuc	200	174	202	176	33	174	41	3-148 / CD20xCD3 / HLHL
215nuc	202	174	200	176	41	174	33	3-148 / CD20xCD3 / LHLH
216nuc	200	174	202	176	41	174	33	3-148 / CD20xCD3 / HLLH
217nuc	57	174	49	176	200	174	202	3-190 / CD3xCD20 / LHHL

218nuc	49	174	57	176	200	174	202	3-190 / CD3xCD20 / HLHL
219nuc	57	174	49	176	202	174	200	3-190 / CD3xCD20 / LHLH
220nuc	49	174	57	176	202	174	200	3-190 / CD3xCD20 / HLLH
221nuc	202	174	200	176	49	174	57	3-190 / CD20xCD3 / LHHL
222nuc	200	174	202	176	49	174	57	3-190 / CD20xCD3 / HLHL
223nuc	202	174	200	176	57	174	49	3-190 / CD20xCD3 / LHLH
224nuc	200	174	202	176	57	174	49	3-190 / CD20xCD3 / HLLH
225nuc	73	174	65	176	200	174	202	3-271 / CD3xCD20 / LHHL
226nuc	65	174	73	176	200	174	202	3-271 / CD3xCD20 / HLHL
227nuc	73	174	65	176	202	174	200	3-271 / CD3xCD20 / LHLH
228nuc	65	174	73	176	202	174	200	3-271 / CD3xCD20 / HLLH
229nuc	202	174	200	176	65	174	73	3-271 / CD20xCD3 / LHHL
230nuc	200	174	202	176	65	174	73	3-271 / CD20xCD3 / HLHL
231nuc	202	174	200	176	73	174	65	3-271 / CD20xCD3 / LHLH
232nuc	200	174	202	176	73	174	65	3-271 / CD20xCD3 / HLLH
233nuc	89	174	81	176	200	174	202	3-550 / CD3xCD20 / LHHL
234nuc	81	174	89	176	200	174	202	3-550 / CD3xCD20 / HLHL
235nuc	89	174	81	176	202	174	200	3-550 / CD3xCD20 / LHLH
236nuc	81	174	89	176	202	174	200	3-550 / CD3xCD20 / HLLH
237nuc	202	174	200	176	81	174	89	3-550 / CD20xCD3 / LHHL
238nuc	200	174	202	176	81	174	89	3-550 / CD20xCD3 / HLHL
239nuc	202	174	200	176	89	174	81	3-550 / CD20xCD3 / LHLH
240nuc	200	174	202	176	89	174	81	3-550 / CD20xCD3 / HLLH
241nuc	105	174	97	176	200	174	202	4-10 / CD3xCD20 / LHHL
242nuc	97	174	105	176	200	174	202	4-10 / CD3xCD20 / HLHL
243nuc	105	174	97	176	202	174	200	4-10 / CD3xCD20 / LHLH
244nuc	97	174	105	176	202	174	200	4-10 / CD3xCD20 / HLLH
245nuc	202	174	200	176	97	174	105	4-10 / CD20xCD3 / LHHL
246nuc	200	174	202	176	97	174	105	4-10 / CD20xCD3 / HLHL
247nuc	202	174	200	176	105	174	97	4-10 / CD20xCD3 / LHLH

248nuc	200	174	202	176	105	174	97	4-10 / CD20xCD3 / HLLH
249nuc	121	174	113	176	200	174	202	4-48 / CD3xCD20 / LHHL
250nuc	113	174	121	176	200	174	202	4-48 / CD3xCD20 / HLHL
251nuc	121	174	113	176	202	174	200	4-48 / CD3xCD20 / LHLH
252nuc	113	174	121	176	202	174	200	4-48 / CD3xCD20 / HLLH
253nuc	202	174	200	176	113	174	121	4-48 / CD20xCD3 / LHHL
254nuc	200	174	202	176	113	174	121	4-48 / CD20xCD3 / HLHL
255nuc	202	174	200	176	121	174	113	4-48 / CD20xCD3 / LHLH
256nuc	200	174	202	176	121	174	113	4-48 / CD20xCD3 / HLLH

Nucleic acid constructs are as defined in Tables 1, 3, 5 and 7. Each nucleic acid construct in each of Tables 1, 3, 5 and 7 comprises 7 distinct nucleic acid modules, denoted A-G. Nucleic acid modules A-G are directly and covalently linked to one another in a single contiguous nucleotide chain by phosphate glycoside bonds in the order A-B-C-D-E-F-G, with nucleic acid module A at the 5'-end and nucleic acid module G at the 3'-end of a respective nucleic acid construct. Nucleic acid modules A, C, E and G denote encoding regions for antibody variable domains which can be either VH or VL domains of antibodies having specificity for different antigens. Each construct comprises nucleic acid modules encoding a VH and VL region from a human antibody or fragment thereof having specificity for human CD3 as well as a VH and VL region from an antibody or fragment thereof having specificity for one of the human antigens CD19, EpCAM, CCR5 or CD20.

If nucleic acid module A encodes a VH antibody domain, then nucleic acid module C encodes a VL protein domain, and vice versa. If nucleic acid module E encodes a VH antibody domain, then nucleic acid module G encodes a VL protein domain, and vice versa.

Nucleic acid molecules encoding VH domains of human antibodies or fragments thereof having specificity for the human CD3 antigen can be selected from the sequences as set out in SEQ ID NOs: 1, 17, 33, 49, 65, 81, 97 or 113. Nucleic acid

molecules encoding VL domains of human antibodies or fragments thereof having specificity for the human CD3 antigen can be selected from the sequences as set out in SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105, 121. Nucleic acid molecules encoding VH and VL domains of an antibody or fragment thereof having specificity for the CD19 antigen have the nucleic acid sequences as set out in SEQ ID NOs: 129 and 131, respectively. Nucleic acid molecules encoding VH and VL domains of an antibody or fragment thereof having specificity for the EpCAM antigen have the nucleic acid sequences as set out in SEQ ID NOs: 133 and 135, respectively. Nucleic acid molecules encoding VH and VL domains of an antibody or fragment thereof having specificity for the CCR5 antigen have the nucleic acid sequences as set out in SEQ ID NOs: 196 and 198, respectively. Nucleic acid molecules encoding VH and VL domains of an antibody or fragment thereof having specificity for the CD20 antigen have the nucleic acid sequences as set out in SEQ ID NOs: 200 and 202, respectively.

Pairs of nucleic acids encoding antibody variable domains denoted by the nucleic acid module pairs A/C and E/G are joined by additional linking nucleic acid modules, wherein nucleic acid module B serves to directly link the module pair A/C and nucleic acid module F serves to directly link the module pair E/G. Nucleic acid modules B and F each have the nucleotide sequence as set out in SEQ ID NO: 174.

The combination of nucleic acid modules A-B-C and the combination of nucleic acid modules E-F-G each respectively constitute one scFv fragment of an antibody having specificity for either the human CD3 antigen or for any of the human antigens CD19, EpCAM, CCR5 or CD20. The respective groups of nucleic acid modules A-B-C and E-F-G are connected to one another through nucleic acid module D, having the nucleotide sequence as set out in SEQ ID NO: 176. Nucleic acid module D serves to connect the 3'-end of nucleic acid module C with the 5'-end of nucleic acid module E.

Especially preferred nucleic acid constructs encoding bispecific single chain binding molecules comprising human anti-CD3 portions are (with corresponding SEQ ID NOs in parentheses) 20nuc (SEQ ID NO: 205), 21nuc (SEQ ID NO: 215), 28nuc (SEQ ID NO: 207), 29nuc (SEQ ID NO: 217), 36nuc (SEQ ID NO: 209), 37nuc (SEQ ID NO: 219), 52nuc (SEQ ID NO: 211), 53nuc (SEQ ID NO: 221), 60nuc (SEQ ID NO: 213), 61nuc (SEQ ID NO: 223), 82nuc (SEQ ID NO: 225), 85nuc (SEQ ID NO: 235), 90nuc (SEQ ID NO: 227), 93nuc (SEQ ID NO: 237), 98nuc (SEQ ID NO: 229), 101nuc (SEQ ID NO: 239), 114nuc (SEQ ID NO: 231), 117nuc (SEQ ID NO: 241), 122nuc (SEQ ID NO: 233), 125nuc (SEQ ID NO: 243), 149nuc (SEQ ID NO: 251), 157nuc (SEQ ID NO: 249), 213nuc (SEQ ID NO: 247) and 221nuc (SEQ ID NO: 245).

Proteinaceous constructs as encoded, inter alia, by the nucleic acid molecules shown in Tables 1, 3, 5 and 7 (as detailed above) are shown and illustrated in the corresponding tables 2, 4, 6 and 8.

Table 2:

Construct	SEQ ID NO in construct portion ...							h anti-hCD3 construct / Specificity (N -> C) / Domain Arrangement
	A	B	C	D	E	F	G	
1prot	10	175	2	177	130	175	132	3-106 / CD3xCD19 / LHHL
2prot	2	175	10	177	130	175	132	3-106 / CD3xCD19 / HLHL
3prot	10	175	2	177	132	175	130	3-106 / CD3xCD19 / LHLH
4prot	2	175	10	177	132	175	130	3-106 / CD3xCD19 / HLLH
5prot	132	175	130	177	2	175	10	3-106 / CD19xCD3 / LHHL
6prot	130	175	132	177	2	175	10	3-106 / CD19xCD3 / HLHL
7prot	132	175	130	177	10	175	2	3-106 / CD19xCD3 / LHLH
8prot	130	175	132	177	10	175	2	3-106 / CD19xCD3 / HLLH
9prot	26	175	18	177	130	175	132	3-114 / CD3xCD19 / LHHL
10prot	18	175	26	177	130	175	132	3-114 / CD3xCD19 / HLHL

11prot	26	175	18	177	132	175	130	3-114 / CD3xCD19 / LHLH
12prot	18	175	26	177	132	175	130	3-114 / CD3xCD19 / HLLH
13prot	132	175	130	177	18	175	26	3-114 / CD19xCD3 / LHHL
14prot	130	175	132	177	18	175	26	3-114 / CD19xCD3 / HLHL
15prot	132	175	130	177	26	175	18	3-114 / CD19xCD3 / LHLH
16prot	130	175	132	177	26	175	18	3-114 / CD19xCD3 / HLLH
17prot	42	175	34	177	130	175	132	3-148 / CD3xCD19 / LHHL
18prot	34	175	42	177	130	175	132	3-148 / CD3xCD19 / HLHL
19prot	42	175	34	177	132	175	130	3-148 / CD3xCD19 / LHLH
20prot	34	175	42	177	132	175	130	3-148 / CD3xCD19 / HLLH
21prot	132	175	130	177	34	175	42	3-148 / CD19xCD3 / LHHL
22prot	130	175	132	177	34	175	42	3-148 / CD19xCD3 / HLHL
23prot	132	175	130	177	42	175	34	3-148 / CD19xCD3 / LHLH
24prot	130	175	132	177	42	175	34	3-148 / CD19xCD3 / HLLH
25prot	58	175	50	177	130	175	132	3-190 / CD3xCD19 / LHHL
26prot	50	175	58	177	130	175	132	3-190 / CD3xCD19 / HLHL
27prot	58	175	50	177	132	175	130	3-190 / CD3xCD19 / LHLH
28prot	50	175	58	177	132	175	130	3-190 / CD3xCD19 / HLLH
29prot	132	175	130	177	50	175	58	3-190 / CD19xCD3 / LHHL
30prot	130	175	132	177	50	175	58	3-190 / CD19xCD3 / HLHL
31prot	132	175	130	177	58	175	50	3-190 / CD19xCD3 / LHLH
32prot	130	175	132	177	58	175	50	3-190 / CD19xCD3 / HLLH
33prot	74	175	66	177	130	175	132	3-271 / CD3xCD19 / LHHL
34prot	66	175	74	177	130	175	132	3-271 / CD3xCD19 / HLHL
35prot	74	175	66	177	132	175	130	3-271 / CD3xCD19 / LHLH
36prot	66	175	74	177	132	175	130	3-271 / CD3xCD19 / HLLH
37prot	132	175	130	177	66	175	74	3-271 / CD19xCD3 / LHHL
38prot	130	175	132	177	66	175	74	3-271 / CD19xCD3 / HLHL
39prot	132	175	130	177	74	175	66	3-271 / CD19xCD3 / LHLH
40prot	130	175	132	177	74	175	66	3-271 / CD19xCD3 / HLLH

41prot	90	175	82	177	130	175	132	3-550 / CD3xCD19 / LHHL
42prot	82	175	90	177	130	175	132	3-550 / CD3xCD19 / HLHL
43prot	90	175	82	177	132	175	130	3-550 / CD3xCD19 / LHLH
44prot	82	175	90	177	132	175	130	3-550 / CD3xCD19 / HLLH
45prot	132	175	130	177	82	175	90	3-550 / CD19xCD3 / LHHL
46prot	130	175	132	177	82	175	90	3-550 / CD19xCD3 / HLHL
47prot	132	175	130	177	90	175	82	3-550 / CD19xCD3 / LHLH
48prot	130	175	132	177	90	175	82	3-550 / CD19xCD3 / HLLH
49prot	106	175	98	177	130	175	132	4-10 / CD3xCD19 / LHHL
50prot	98	175	106	177	130	175	132	4-10 / CD3xCD19 / HLHL
51prot	106	175	98	177	132	175	130	4-10 / CD3xCD19 / LHLH
52prot	98	175	106	177	132	175	130	4-10 / CD3xCD19 / HLLH
53prot	132	175	130	177	98	175	106	4-10 / CD19xCD3 / LHHL
54prot	130	175	132	177	98	175	106	4-10 / CD19xCD3 / HLHL
55prot	132	175	130	177	106	175	98	4-10 / CD19xCD3 / LHLH
56prot	130	175	132	177	106	175	98	4-10 / CD19xCD3 / HLLH
57prot	122	175	114	177	130	175	132	4-48 / CD3xCD19 / LHHL
58prot	114	175	122	177	130	175	132	4-48 / CD3xCD19 / HLHL
59prot	122	175	114	177	132	175	130	4-48 / CD3xCD19 / LHLH
60prot	114	175	122	177	132	175	130	4-48 / CD3xCD19 / HLLH
61prot	132	175	130	177	114	175	122	4-48 / CD19xCD3 / LHHL
62prot	130	175	132	177	114	175	122	4-48 / CD19xCD3 / HLHL
63prot	132	175	130	177	122	175	114	4-48 / CD19xCD3 / LHLH
64prot	130	175	132	177	122	175	114	4-48 / CD19xCD3 / HLLH

Table 4:

Construct	SEQ ID NO in construct portion ...							h anti-hCD3 construct / Specificity (N -> C) / Domain Arrangement
	A	B	C	D	E	F	G	
65prot	10	175	2	177	134	175	136	3-106 / CD3xEpCAM / LHHL
66prot	2	175	10	177	134	175	136	3-106 / CD3xEpCAM / HLHL
67prot	10	175	2	177	136	175	134	3-106 / CD3xEpCAM / LHLH
68prot	2	175	10	177	136	175	134	3-106 / CD3xEpCAM / HLLH
69prot	136	175	134	177	2	175	10	3-106 / EpCAMxCD3 / LHHL
70prot	134	175	136	177	2	175	10	3-106 / EpCAMxCD3 / HLHL
71prot	136	175	134	177	10	175	2	3-106 / EpCAMxCD3 / LHLH
72prot	134	175	136	177	10	175	2	3-106 / EpCAMxCD3 / HLLH
73prot	26	175	18	177	134	175	136	3-114 / CD3xEpCAM / LHHL
74prot	18	175	26	177	134	175	136	3-114 / CD3xEpCAM / HLHL
75prot	26	175	18	177	136	175	134	3-114 / CD3xEpCAM / LHLH
76prot	18	175	26	177	136	175	134	3-114 / CD3xEpCAM / HLLH
77prot	136	175	134	177	18	175	26	3-114 / EpCAMxCD3 / LHHL
78prot	134	175	136	177	18	175	26	3-114 / EpCAMxCD3 / HLHL
79prot	136	175	134	177	26	175	18	3-114 / EpCAMxCD3 / LHLH
80prot	134	175	136	177	26	175	18	3-114 / EpCAMxCD3 / HLLH
81prot	42	175	34	177	134	175	136	3-148 / CD3xEpCAM / LHHL
82prot	34	175	42	177	134	175	136	3-148 / CD3xEpCAM / HLHL
83prot	42	175	34	177	136	175	134	3-148 / CD3xEpCAM / LHLH
84prot	34	175	42	177	136	175	134	3-148 / CD3xEpCAM / HLLH
85prot	136	175	134	177	34	175	42	3-148 / EpCAMxCD3 / LHHL
86prot	134	175	136	177	34	175	42	3-148 / EpCAMxCD3 / HLHL
87prot	136	175	134	177	42	175	34	3-148 / EpCAMxCD3 / LHLH
88prot	134	175	136	177	42	175	34	3-148 / EpCAMxCD3 / HLLH
89prot	58	175	50	177	134	175	136	3-190 / CD3xEpCAM / LHHL

90prot	50	175	58	177	134	175	136	3-190 / CD3xEpCAM / HLHL
91prot	58	175	50	177	136	175	134	3-190 / CD3xEpCAM / LHLH
92prot	50	175	58	177	136	175	134	3-190 / CD3xEpCAM / HLLH
93prot	136	175	134	177	50	175	58	3-190 / EpCAMxCD3 / LHHL
94prot	134	175	136	177	50	175	58	3-190 / EpCAMxCD3 / HLHL
95prot	136	175	134	177	58	175	50	3-190 / EpCAMxCD3 / LHLH
96prot	134	175	136	177	58	175	50	3-190 / EpCAMxCD3 / HLLH
97prot	74	175	66	177	134	175	136	3-271 / CD3xEpCAM / LHHL
98prot	66	175	74	177	134	175	136	3-271 / CD3xEpCAM / HLHL
99prot	74	175	66	177	136	175	134	3-271 / CD3xEpCAM / LHLH
100prot	66	175	74	177	136	175	134	3-271 / CD3xEpCAM / HLLH
101prot	136	175	134	177	66	175	74	3-271 / EpCAMxCD3 / LHHL
102prot	134	175	136	177	66	175	74	3-271 / EpCAMxCD3 / HLHL
103prot	136	175	134	177	74	175	66	3-271 / EpCAMxCD3 / LHLH
104prot	134	175	136	177	74	175	66	3-271 / EpCAMxCD3 / HLLH
105prot	90	175	82	177	134	175	136	3-550 / CD3xEpCAM / LHHL
106prot	82	175	90	177	134	175	136	3-550 / CD3xEpCAM / HLHL
107prot	90	175	82	177	136	175	134	3-550 / CD3xEpCAM / LHLH
108prot	82	175	90	177	136	175	134	3-550 / CD3xEpCAM / HLLH
109prot	136	175	134	177	82	175	90	3-550 / EpCAMxCD3 / LHHL
110prot	134	175	136	177	82	175	90	3-550 / EpCAMxCD3 / HLHL
111prot	136	175	134	177	90	175	82	3-550 / EpCAMxCD3 / LHLH
112prot	134	175	136	177	90	175	82	3-550 / EpCAMxCD3 / HLLH
113prot	106	175	98	177	134	175	136	4-10 / CD3xEpCAM / LHHL
114prot	98	175	106	177	134	175	136	4-10 / CD3xEpCAM / HLHL
115prot	106	175	98	177	136	175	134	4-10 / CD3xEpCAM / LHLH
116prot	98	175	106	177	136	175	134	4-10 / CD3xEpCAM / HLLH
117prot	136	175	134	177	98	175	106	4-10 / EpCAMxCD3 / LHHL
118prot	134	175	136	177	98	175	106	4-10 / EpCAMxCD3 / HLHL
119prot	136	175	134	177	106	175	98	4-10 / EpCAMxCD3 / LHLH

120prot	134	175	136	177	106	175	98	4-10 / EpCAMxCD3 / HLLH
121prot	122	175	114	177	134	175	136	4-48 / CD3xEpCAM / LHHL
122prot	114	175	122	177	134	175	136	4-48 / CD3xEpCAM / HLHL
123prot	122	175	114	177	136	175	134	4-48 / CD3xEpCAM / LHLH
124prot	114	175	122	177	136	175	134	4-48 / CD3xEpCAM / HLLH
125prot	136	175	134	177	114	175	122	4-48 / EpCAMxCD3 / LHHL
126prot	134	175	136	177	114	175	122	4-48 / EpCAMxCD3 / HLHL
127prot	136	175	134	177	122	175	114	4-48 / EpCAMxCD3 / LHLH
128prot	134	175	136	177	122	175	114	4-48 / EpCAMxCD3 / HLLH

Table 6:

Construct	SEQ ID NO in construct portion ...							h anti-hCD3 construct / Specificity (N -> C) / Domain Arrangement
	A	B	C	D	E	F	G	
129prot	10	175	2	177	197	175	199	3-106 / CD3xCCR5 / LHHL
130prot	2	175	10	177	197	175	199	3-106 / CD3xCCR5 / HLHL
131prot	10	175	2	177	199	175	197	3-106 / CD3xCCR5 / LHLH
132prot	2	175	10	177	199	175	197	3-106 / CD3xCCR5 / HLLH
133prot	199	175	197	177	2	175	10	3-106 / CCR5xCD3 / LHHL
134prot	197	175	199	177	2	175	10	3-106 / CCR5xCD3 / HLHL
135prot	199	175	197	177	10	175	2	3-106 / CCR5xCD3 / LHLH
136prot	197	175	199	177	10	175	2	3-106 / CCR5xCD3 / HLLH
137prot	26	175	18	177	197	175	199	3-114 / CD3xCCR5 / LHHL
138prot	18	175	26	177	197	175	199	3-114 / CD3xCCR5 / HLHL
139prot	26	175	18	177	199	175	197	3-114 / CD3xCCR5 / LHLH
140prot	18	175	26	177	199	175	197	3-114 / CD3xCCR5 / HLLH
141prot	199	175	197	177	18	175	26	3-114 / CCR5xCD3 / LHHL
142prot	197	175	199	177	18	175	26	3-114 / CCR5xCD3 / HLHL
143prot	199	175	197	177	26	175	18	3-114 / CCR5xCD3 / LHLH

144prot	197	175	199	177	26	175	18	3-114 / CCR5xCD3 / HLLH
145prot	42	175	34	177	197	175	199	3-148 / CD3xCCR5 / LHHL
146prot	34	175	42	177	197	175	199	3-148 / CD3xCCR5 / HLHL
147prot	42	175	34	177	199	175	197	3-148 / CD3xCCR5 / LHLH
148prot	34	175	42	177	199	175	197	3-148 / CD3xCCR5 / HLLH
149prot	199	175	197	177	34	175	42	3-148 / CCR5xCD3 / LHHL
150prot	197	175	199	177	34	175	42	3-148 / CCR5xCD3 / HLHL
151prot	199	175	197	177	42	175	34	3-148 / CCR5xCD3 / LHLH
152prot	197	175	199	177	42	175	34	3-148 / CCR5xCD3 / HLLH
153prot	58	175	50	177	197	175	199	3-190 / CD3xCCR5 / LHHL
154prot	50	175	58	177	197	175	199	3-190 / CD3xCCR5 / HLHL
155prot	58	175	50	177	199	175	197	3-190 / CD3xCCR5 / LHLH
156prot	50	175	58	177	199	175	197	3-190 / CD3xCCR5 / HLLH
157prot	199	175	197	177	50	175	58	3-190 / CCR5xCD3 / LHHL
158prot	197	175	199	177	50	175	58	3-190 / CCR5xCD3 / HLHL
159prot	199	175	197	177	58	175	50	3-190 / CCR5xCD3 / LHLH
160prot	197	175	199	177	58	175	50	3-190 / CCR5xCD3 / HLLH
161prot	74	175	66	177	197	175	199	3-271 / CD3xCCR5 / LHHL
162prot	66	175	74	177	197	175	199	3-271 / CD3xCCR5 / HLHL
163prot	74	175	66	177	199	175	197	3-271 / CD3xCCR5 / LHLH
164prot	66	175	74	177	199	175	197	3-271 / CD3xCCR5 / HLLH
165prot	199	175	197	177	66	175	74	3-271 / CCR5xCD3 / LHHL
166prot	197	175	199	177	66	175	74	3-271 / CCR5xCD3 / HLHL
167prot	199	175	197	177	74	175	66	3-271 / CCR5xCD3 / LHLH
168prot	197	175	199	177	74	175	66	3-271 / CCR5xCD3 / HLLH
169prot	90	175	82	177	197	175	199	3-550 / CD3xCCR5 / LHHL
170prot	82	175	90	177	197	175	199	3-550 / CD3xCCR5 / HLHL
171prot	90	175	82	177	199	175	197	3-550 / CD3xCCR5 / LHLH
172prot	82	175	90	177	199	175	197	3-550 / CD3xCCR5 / HLLH
173prot	199	175	197	177	82	175	90	3-550 / CCR5xCD3 / LHHL

174prot	197	175	199	177	82	175	90	3-550 / CCR5xCD3 / HLHL
175prot	199	175	197	177	90	175	82	3-550 / CCR5xCD3 / LHLH
176prot	197	175	199	177	90	175	82	3-550 / CCR5xCD3 / HLLH
177prot	106	175	98	177	197	175	199	4-10 / CD3xCCR5 / LHHL
178prot	98	175	106	177	197	175	199	4-10 / CD3xCCR5 / HLHL
179prot	106	175	98	177	199	175	197	4-10 / CD3xCCR5 / LHLH
180prot	98	175	106	177	199	175	197	4-10 / CD3xCCR5 / HLLH
181prot	199	175	197	177	98	175	106	4-10 / CCR5xCD3 / LHHL
182prot	197	175	199	177	98	175	106	4-10 / CCR5xCD3 / HLHL
183prot	199	175	197	177	106	175	98	4-10 / CCR5xCD3 / LHLH
184prot	197	175	199	177	106	175	98	4-10 / CCR5xCD3 / HLLH
185prot	122	175	114	177	197	175	199	4-48 / CD3xCCR5 / LHHL
186prot	114	175	122	177	197	175	199	4-48 / CD3xCCR5 / HLHL
187prot	122	175	114	177	199	175	197	4-48 / CD3xCCR5 / LHLH
188prot	114	175	122	177	199	175	197	4-48 / CD3xCCR5 / HLLH
189prot	199	175	197	177	114	175	122	4-48 / CCR5xCD3 / LHHL
190prot	197	175	199	177	114	175	122	4-48 / CCR5xCD3 / HLHL
191prot	199	175	197	177	122	175	114	4-48 / CCR5xCD3 / LHLH
192prot	197	175	199	177	122	175	114	4-48 / CCR5xCD3 / HLLH

Table 8:

Construct	SEQ ID NO in construct portion ...							h anti-hCD3 construct / Specificity (N -> C) / Domain Arrangement
	A	B	C	D	E	F	G	
193prot	10	175	2	177	201	175	203	3-106 / CD3xCD20 / LHHL
194prot	2	175	10	177	201	175	203	3-106 / CD3xCD20 / HLHL
195prot	10	175	2	177	203	175	201	3-106 / CD3xCD20 / LHLH
196prot	2	175	10	177	203	175	201	3-106 / CD3xCD20 / HLLH
197prot	203	175	201	177	2	175	10	3-106 / CD20xCD3 / LHHL

198prot	201	175	203	177	2	175	10	3-106 / CD20xCD3 / HLHL
199prot	203	175	201	177	10	175	2	3-106 / CD20xCD3 / LHLH
200prot	201	175	203	177	10	175	2	3-106 / CD20xCD3 / HLLH
201prot	26	175	18	177	201	175	203	3-114 / CD3xCD20 / LHHL
202prot	18	175	26	177	201	175	203	3-114 / CD3xCD20 / HLHL
203prot	26	175	18	177	203	175	201	3-114 / CD3xCD20 / LHLH
204prot	18	175	26	177	203	175	201	3-114 / CD3xCD20 / HLLH
205prot	203	175	201	177	18	175	26	3-114 / CD20xCD3 / LHHL
206prot	201	175	203	177	18	175	26	3-114 / CD20xCD3 / HLHL
207prot	203	175	201	177	26	175	18	3-114 / CD20xCD3 / LHLH
208prot	201	175	203	177	26	175	18	3-114 / CD20xCD3 / HLLH
209prot	42	175	34	177	201	175	203	3-148 / CD3xCD20 / LHHL
210prot	34	175	42	177	201	175	203	3-148 / CD3xCD20 / HLHL
211prot	42	175	34	177	203	175	201	3-148 / CD3xCD20 / LHLH
212prot	34	175	42	177	203	175	201	3-148 / CD3xCD20 / HLLH
213prot	203	175	201	177	34	175	42	3-148 / CD20xCD3 / LHHL
214prot	201	175	203	177	34	175	42	3-148 / CD20xCD3 / HLHL
215prot	203	175	201	177	42	175	34	3-148 / CD20xCD3 / LHLH
216prot	201	175	203	177	42	175	34	3-148 / CD20xCD3 / HLLH
217prot	58	175	50	177	201	175	203	3-190 / CD3xCD20 / LHHL
218prot	50	175	58	177	201	175	203	3-190 / CD3xCD20 / HLHL
219prot	58	175	50	177	203	175	201	3-190 / CD3xCD20 / LHLH
220prot	50	175	58	177	203	175	201	3-190 / CD3xCD20 / HLLH
221prot	203	175	201	177	50	175	58	3-190 / CD20xCD3 / LHHL
222prot	201	175	203	177	50	175	58	3-190 / CD20xCD3 / HLHL
223prot	203	175	201	177	58	175	50	3-190 / CD20xCD3 / LHLH
224prot	201	175	203	177	58	175	50	3-190 / CD20xCD3 / HLLH
225prot	74	175	66	177	201	175	203	3-271 / CD3xCD20 / LHHL
226prot	66	175	74	177	201	175	203	3-271 / CD3xCD20 / HLHL
227prot	74	175	66	177	203	175	201	3-271 / CD3xCD20 / LHLH

228prot	66	175	74	177	203	175	201	3-271 / CD3xCD20 / HLLH
229prot	203	175	201	177	66	175	74	3-271 / CD20xCD3 / LHHL
230prot	201	175	203	177	66	175	74	3-271 / CD20xCD3 / HLHL
231prot	203	175	201	177	74	175	66	3-271 / CD20xCD3 / LHLH
232prot	201	175	203	177	74	175	66	3-271 / CD20xCD3 / HLLH
233prot	90	175	82	177	201	175	203	3-550 / CD3xCD20 / LHHL
234prot	82	175	90	177	201	175	203	3-550 / CD3xCD20 / HLHL
235prot	90	175	82	177	203	175	201	3-550 / CD3xCD20 / LHLH
236prot	82	175	90	177	203	175	201	3-550 / CD3xCD20 / HLLH
237prot	203	175	201	177	82	175	90	3-550 / CD20xCD3 / LHHL
238prot	201	175	203	177	82	175	90	3-550 / CD20xCD3 / HLHL
239prot	203	175	201	177	90	175	82	3-550 / CD20xCD3 / LHLH
240prot	201	175	203	177	90	175	82	3-550 / CD20xCD3 / HLLH
241prot	106	175	98	177	201	175	203	4-10 / CD3xCD20 / LHHL
242prot	98	175	106	177	201	175	203	4-10 / CD3xCD20 / HLHL
243prot	106	175	98	177	203	175	201	4-10 / CD3xCD20 / LHLH
244prot	98	175	106	177	203	175	201	4-10 / CD3xCD20 / HLLH
245prot	203	175	201	177	98	175	106	4-10 / CD20xCD3 / LHHL
246prot	201	175	203	177	98	175	106	4-10 / CD20xCD3 / HLHL
247prot	203	175	201	177	106	175	98	4-10 / CD20xCD3 / LHLH
248prot	201	175	203	177	106	175	98	4-10 / CD20xCD3 / HLLH
249prot	122	175	114	177	201	175	203	4-48 / CD3xCD20 / LHHL
250prot	114	175	122	177	201	175	203	4-48 / CD3xCD20 / HLHL
251prot	122	175	114	177	203	175	201	4-48 / CD3xCD20 / LHLH
252prot	114	175	122	177	203	175	201	4-48 / CD3xCD20 / HLLH
253prot	203	175	201	177	114	175	122	4-48 / CD20xCD3 / LHHL
254prot	201	175	203	177	114	175	122	4-48 / CD20xCD3 / HLHL
255prot	203	175	201	177	122	175	114	4-48 / CD20xCD3 / LHLH
256prot	201	175	203	177	122	175	114	4-48 / CD20xCD3 / HLLH

Protein constructs are as defined in Tables 2, 4, 6 and 8. Each protein construct in

each of the Tables 2, 4, 6 and 8 comprises 7 distinct protein modules, denoted A-G. Protein modules A-G are directly and covalently linked to one another in a single contiguous polypeptide chain by peptide bonds in the order A-B-C-D-E-F-G, with protein module A at the N-terminus and protein module G at the C-terminus. Protein modules A, C, E and G denote antibody variable domains which can be either VH or VL domains of antibodies having specificity for the different antigens. Each construct protein modules encoding a VH and VL region from a human antibody or fragment thereof having specificity for human CD3 as well as a VH and VL region from an antibody or fragment thereof having specificity for one of the human antigens CD19, EpCAM, CCR5 or CD20.

If protein module A is a VH antibody domain, then protein module C is a VL protein domain, and vice versa. If protein module E is a VH antibody domain, then protein module G is a VL protein domain, and vice versa.

VH domains of human antibodies or fragments thereof having specificity for the human CD3 antigen can be selected from the amino acid sequences as set out in SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98 or 114. VL domains of human antibodies or fragments thereof having specificity for the human CD3 antigen can be selected from the amino acid sequences as set out in SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106 or 122. Protein molecules encoding VH and VL domains of an antibody or fragment thereof having specificity for the CD19 antigen have the amino acid sequences as set out in SEQ ID NOs: 130 and 132, respectively. Protein molecules encoding VH and VL domains of an antibody or fragment thereof having specificity for the EpCAM antigen have the amino acid sequences as set out in SEQ ID NOs: 134 and 136, respectively. Protein molecules encoding VH and VL domains of an antibody or fragment thereof having specificity for the CCR5 antigen have the amino acid sequences as set out in SEQ ID NOs: 197 and 199, respectively. Protein molecules encoding VH and VL domains of an antibody or fragment thereof having specificity for the CD20 antigen have the amino acid sequences as set out in SEQ ID NOs: 201 and 203, respectively.

Pairs of antibody variable domains denoted by the protein module pairs A/C and E/G are joined by additional linking protein modules, wherein protein module B serves to directly link the module pair A/C and protein module F serves to directly link the module pair E/G. Protein modules B and F each have the amino acid sequence as set out in SEQ ID NO: 175.

The combination of protein modules A-B-C and the combination of protein modules E-F-G each respectively constitute one scFv fragment of an antibody having specificity for either the human CD3 antigen or for any of the human antigens CD19, EpCAM, CCR5 or CD20. The respective groups of protein modules A-B-C and E-F-G are connected to each other through protein module D, having the amino acid sequence as set out in SEQ ID NO: 177. Protein module D serves to connect the C-terminal end of protein module C with the N-terminal end of protein module E.

Especially preferred bispecific single chain binding molecules comprising human anti-CD3 portions are (with corresponding SEQ ID NOs in parentheses): 20prot (SEQ ID NO: 206), 21prot (SEQ ID NO: 216), 28prot (SEQ ID NO: 208), 29prot (SEQ ID NO: 218), 36prot (SEQ ID NO: 210), 37prot (SEQ ID NO: 220), 52prot (SEQ ID NO: 212), 53prot (SEQ ID NO: 222), 60prot (SEQ ID NO: 214), 61prot (SEQ ID NO: 224), 82prot (SEQ ID NO: 226), 85prot (SEQ ID NO: 236), 90prot (SEQ ID NO: 228), 93prot (SEQ ID NO: 238), 98prot (SEQ ID NO: 230), 101prot (SEQ ID NO: 240), 114prot (SEQ ID NO: 232), 117prot (SEQ ID NO: 242), 122prot (SEQ ID NO: 234), 125prot (SEQ ID NO: 244), 149prot (SEQ ID NO: 252), 157prot (SEQ ID NO: 250), 213prot (SEQ ID NO: 248) and 221prot (SEQ ID NO: 246).

Accordingly, in one embodiment of the inventive human binding molecule specifically binding to human CD3/human CD3 complex comprises a further antigen binding site, said further antigen binding site specifically binds to/interacts with the CD19 molecule.

Preferably, the corresponding human binding molecule of the invention comprises an amino acid sequence selected from the group of:

(a) an amino acid sequence corresponding to construct 1prot to 64prot of table 2 herein above;

(b) (an amino acid sequence encoded by a nucleic acid sequence corresponding to construct 1nuc to 64nuc of table 1 herein above;

(c) an amino acid sequence encoded by a nucleic acid sequence hybridizing with the complementary strand of a nucleic acid sequence as defined in (b) under stringent hybridization conditions; and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c).

It is of note that the nucleic acid sequences referred to in (c) herein above specifically code for human anti-human CD3 bispecific constructs with a second specificity for CD19, preferably human CD19.

Particular preferred human anti-human CD3xCD19 constructs (nucleic acid and protein) are depicted in SEQ ID NOs: 205, 206, 207, 208, 209, 210, 211, 212, 213 and 214. Also envisaged are constructs in the format CD19x human anti-human CD3. Illustrative and preferred examples of said constructs (nucleic acid and protein) are shown in SEQ ID NOs.: 215, 216, 217, 218, 219, 220, 221, 222, 223 and 224.

In an alternative embodiment of the human binding molecule of the invention said further antigen binding site specifically binds to/interacts with the EpCAM molecule. The term "EpCAM" defines a cell surface molecule also known as 17-1, GA733, CO17-1a, EGP, KS1-4, KSA,ESA, Epithelial cell adhesion molecule, etc. (see, e.g. Helrich, Int. J. Cancer 76 (1998), 232-9; Staib, Int. J. Cancer 92 (2001), 79-87).

Accordingly, in one embodiment of the inventive human binding molecule specifically binding to human CD3/human CD3 complex comprises a further antigen binding site, said further antigen binding site specifically binds to/interacts with the EpCAM molecule. Preferably, the corresponding human binding molecule comprises an amino acid sequence selected from the group of:

(a) an amino acid sequence corresponding to construct 65prot to 128prot of table 4 as shown above;

(b) an amino acid sequence encoded by a nucleic acid sequence corresponding to construct 65nuc to 128nuc of table 3 as shown above;

(c) an amino acid sequence encoded by a nucleic acid sequence hybridizing with the complementary strand of a nucleic acid sequence as defined in (b) under stringent hybridization conditions; and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c).

It is of note that the nucleic acid sequences referred to in (c) herein above specifically code for human anti-human CD3 bispecific constructs with a second specificity for EpCAM, preferably human EpCAM.

Particular preferred human anti-human CD3xEpCAM constructs (nucleic acid and protein) are depicted in SEQ ID NOs: 225, 226, 227, 228, 229, 230, 231, 232, 233 and 234. Also envisaged are constructs in the format EpCAM x human anti-human CD3. Illustrative and preferred examples of said constructs (nucleic acid and protein) are shown in SEQ ID NOs.: 235, 236, 237, 238, 239, 240, 241, 242, 243 or 244.

In a further alternative embodiment of the human binding molecule of the invention, it comprises a further antigen binding site, said further antigen binding site being capable of specifically binding to/interacting with the CCR5 molecule. Therefore, it is envisaged that a human binding molecule of the invention comprises an amino acid sequence selected from the group of:

(a) an amino acid sequence corresponding to construct 129prot to 192prot of table 6 herein above;

(b) an amino acid sequence encoded by a nucleic acid sequence corresponding to construct 129nuc to 192nuc of table 5 herein above;

(c) an amino acid sequence encoded by a nucleic acid sequence hybridizing

with the complementary strand of a nucleic acid sequence as defined in (b) under stringent hybridization conditions; and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c).

It is of note that the nucleic acid sequences referred to in (c) herein above specifically code for human anti-human CD3 bispecific constructs with a second specificity for CCR5.

Particular preferred human anti-human CD3xCCR5 constructs (nucleic acid and protein) are depicted in SEQ ID NOs: 249, 250, 251 and 252.

Moreover, in an alternative embodiment of the human binding molecule of the invention, having at least two binding specificities, comprises a binding specificity for human CD3/CD3 complex and a further antigen binding site, further antigen binding site specifically binding to/interacting with the CD20 molecule, preferably the human CD20 molecule. Accordingly, it is also envisaged that a human binding molecule of the invention comprises an amino acid sequence selected from the group of:

(a) an amino acid sequence corresponding to construct 193prot to 256prot of table 8 shown herein above;

(b) an amino acid sequence encoded by a nucleic acid sequence corresponding to construct 193nuc to 256nuc of table 7 shown herein above;

(c) an amino acid sequence encoded by a nucleic acid sequence hybridizing with the complementary strand of a nucleic acid sequence as defined in (b) under stringent hybridization conditions; and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c).

It is of note that the nucleic acid sequences referred to in (c) herein above specifically code for human anti-human CD3 bispecific constructs with a second

specificity for CD20, preferably human CD20.

Particular preferred constructs (nucleic acid and protein) in the format CD20x human anti-human CD3 are shown in SEQ ID NOs.: 245, 246, 247 and 248.

The invention also relates to an above characterized human binding molecule, wherein said binding molecule is obtainable by a method of the invention.

Further, the invention relates to a nucleic acid sequence encoding a human binding molecule described herein. Said nucleic acid molecule may be a naturally nucleic acid molecule as well as a recombinant nucleic acid molecule. The nucleic acid molecule of the invention may, therefore, be of natural origin, synthetic or semi-synthetic. It may comprise DNA, RNA as well as PNA and it may be a hybrid thereof.

Thus, the present invention relates, in a preferred embodiment, to a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding the mature form of a protein comprising the amino acid sequence of human binding molecule of the invention, preferably as given in SEQ ID Nos: 181, 183, 185, 187, 189, 191, 193, 195, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250 or 252;

(b) a nucleotide sequence comprising or consisting of the DNA sequence as given in SEQ ID NOs: 180, 182, 184, 186, 188, 190, 192, 194, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249 or 251;

(c) a nucleotide sequence hybridizing with the complementary strand of a nucleotide sequence as defined in (b) under stringent hybridization conditions;

(d) a nucleotide sequence encoding a protein derived from the protein encoded by a nucleotide sequence of (a) or (b) by way of substitution, deletion and/or addition of one or several amino acids of the amino acid sequence encoded

by the nucleotide sequence of (a) or (b);

(e) a nucleotide sequence encoding a protein having an amino acid sequence at least 60 %, preferably 70%, more preferably 80%, most preferably 90% identical to the amino acid sequence encoded by the nucleotide sequence of (a) or (b);

(f) a nucleotide sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (a) to (e);

The above mentioned nucleic acid SEQ ID NOs: 180, 182, 184, 186, 188, 190, 192 and 194 relate to specific human anti-human CD3-binders of the present invention in scFv format. The corresponding protein sequences are shown in SEQ ID NOs: 181, 183, 185, 187, 189, 191, 193 and 195. As detailed above, the SEQ ID NOs: 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250 and 252 relate to exemplified, bispecific protein constructs comprising, as one specificity, the human anti-human CD3 binding molecule of the invention. Corresponding encoding nucleic acid sequences are given in SEQ ID NOs: 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249 or 251, respectively.

The term "mature form of the protein" defines in the context of the present invention a protein translated from its corresponding mRNA and optionally subsequently modified.

The term "hybridizing" has been defined in the context of the present invention herein above.

It is evident to the person skilled in the art that regulatory sequences may be added to the nucleic acid molecule of the invention. For example, promoters, transcriptional enhancers and/or sequences which allow for induced expression of the polynucleotide of the invention may be employed. A suitable inducible system is for example tetracycline-regulated gene expression as described, e.g., by Gossen and Bujard (Proc. Natl. Acad. Sci. USA 89 (1992), 5547-5551) and Gossen et al. (Trends Biotech. 12 (1994), 58-62), or a dexamethasone-inducible gene expression system as described, e.g. by Crook (1989) EMBO J. 8, 513-519 .

Furthermore, it is envisaged for further purposes that nucleic acid molecule may contain, for example, thioester bonds and/or nucleotide analogues. Said modifications may be useful for the stabilization of the nucleic acid molecule against endo- and/or exonucleases in the cell. Said nucleic acid molecules may be transcribed by an appropriate vector containing a chimeric gene which allows for the transcription of said nucleic acid molecule in the cell. In this respect, it is also to be understood that the polynucleotide of the invention can be used for "gene targeting" or "gene therapeutic" approaches. In another embodiment said nucleic acid molecules are labeled. Methods for the detection of nucleic acids are well known in the art, e.g., Southern and Northern blotting, PCR or primer extension. This embodiment may be useful for screening methods for verifying successful introduction of the nucleic acid molecules described above during gene therapy approaches.

Said nucleic acid molecule(s) may be a recombinantly produced chimeric nucleic acid molecule comprising any of the aforementioned nucleic acid molecules either alone or in combination. Preferably, the nucleic acid molecule is part of a vector. Examples for suitable vectors have been described herein above.

Preferably said vector of the invention comprises a nucleic acid sequence which is a regulatory sequence operably linked to said nucleic acid sequence encoding a human binding molecule of the invention.

It is envisaged that the vector of the invention is an expression vector wherein the nucleic acid molecule encodes a human binding molecule of the invention.

The terms "control sequence" and "operably linked", as well as examples for suitable vector systems have been described herein above.

The present invention furthermore relates to host containing at least one vector or at least one nucleic acid molecule of the invention.

Said host may be produced by introducing said at least one vector or at least one nucleic acid molecule into the host. The presence of said at least one vector or at least one nucleic acid molecule in the host may mediate the expression of a gene encoding a human binding molecule of the invention.

The nucleic acid molecule or vector of the invention which is present in the host may either be integrated into the genome of the host or it may be maintained extrachromosomally.

Suitable hosts are discussed herein above. Yet, the host can be any prokaryote or eukaryotic cell. In a preferred embodiment the host is a bacteria, an insect, fungal, plant or animal cell. Preferably it is envisaged that the host of the invention may be a mammalian cell, more preferably a human cell or human cell line. Particularly preferred host cells comprise CHO cells, COS cells, myeloma cell lines like SP2/0 or NS/0.

A method for the production of such host is exemplified in the appended examples.

An alternative embodiment of the invention relates to a process for the production of a human binding molecule of the invention, said process comprising culturing a host of the invention under conditions allowing the expression of the polypeptide construct and recovering the produced polypeptide construct from the culture.

The transformed hosts can be grown in fermentors and cultured according to techniques known in the art to achieve optimal cell growth. The polypeptide of the invention can then be isolated from the growth medium, cellular lysates, or cellular membrane fractions. The isolation and purification of the, e.g., microbially expressed polypeptides of the invention may be by any conventional means such as, for example, preparative chromatographic separations and immunological separations such as those involving the use of monoclonal or polyclonal antibodies directed, e.g., against a tag of the polypeptide of the invention or as described in the appended examples.

The conditions for the culturing of a host which allow the expression are known in the art and discussed herein above. The same holds true for procedures for the purification/recovery of said polypeptide constructs.

The invention also provides for a composition comprising a human binding molecule(s) of the invention or as produced by the method of the invention. The compositions of the invention, which are pharmaceutical compositions may be administered simultaneously or in a non-simultaneous way with an above defined

proteinaceous compound capable of mediating an activation signal for immune effector cells.

In the light of the present invention, said "proteinaceous compounds" providing an activation signal for immune effector cells" may be, e.g. an activation signal for T cells. Preferred formats of proteinaceous compounds comprise bispecifc antibodies and fragments or derivatives thereof, e.g. bispecific scFv. Preferably, said activation signal for T cells may be provided via the T cell receptor (TCR), more preferably via CD3 molecule of the TCR. Proteinaceous compounds can comprise, but are not limited to, scFv fragments specific for CD3, scFv fragments specific for the T cell receptor or superantigens. Superantigens directly bind to certain subfamilies of T cell receptor variable regions in an MHC-independent manner thus mediating the primary T cell activation signal. The proteinaceous compound may also provide an activation signal for an immune effector cell which is a non-T cell. Examples of immune effector cells which are non-T cells comprise, inter alia, B cells and NK cells.

The present invention also relates to compositions which are pharmaceutical compositions comprising these aforementioned human binding molecule(s), nucleic acid molecule(s), vector(s) or host(s) of the invention and, optionally, the described proteinaceous compound capable of an activation signal for immune effector cells.

The compositions of the invention, which are pharmaceutical compositions may be administered simultaneously or in a non-simultaneous way with an above defined proteinaceous compound capable of mediating an activation signal for immune effector cells.

In a further preferred embodiment of the invention the composition, which is a pharmaceutical composition, further comprises suitable formulations of carrier, stabilizers and/or excipients.

In accordance with this invention, the term "pharmaceutical composition" relates to a composition for administration to a patient, preferably a human patient. In preferred embodiment, the pharmaceutical composition comprises a composition for parenteral, intraluminal, intra-arterial, intrathecal or transdermal administration. Also envisaged is direct injection into a tissue, for example into a tumor. It is in particular envisaged that said pharmaceutical composition is administered to a patient via infusion or injection. Administration of the suitable compositions may be effected by different ways, e.g., by intravenous, intraperitoneal, subcutaneous, intramuscular, topical or intradermal administration. The pharmaceutical composition of the present invention may further comprise a pharmaceutically acceptable carrier. Examples of suitable pharmaceutical carriers are well known in the art and include phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions, etc. Compositions comprising such carriers can be formulated by well known conventional methods. These pharmaceutical compositions can be administered to the subject at a suitable dose. The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. A preferred dosage for administration might be in the range of 0.24 µg to 48 mg units per kilogram of body weight per day, preferably 0.24 µg to 24 mg, more preferably 0.24 µg to 2.4 mg even more preferably 0.24 µg to 0.24 µg and most preferably 0.24 µg to 240 µg units per kg body weight per day. Particularly preferred dosages are recited herein below. Progress can be monitored by periodic assessment. Dosages will vary but a preferred dosage for intravenous administration of DNA is from approximately 10^6 to 10^{12} copies of the DNA molecule. The compositions of the invention may be administered locally or systematically. Administration will generally be parenterally, e.g., intravenously; DNA may also be administered directed to the target site, e.g., by biolistic delivery

to an internal or external target site or by catheter to a site in an artery. Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishes, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present such as, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. In addition, the pharmaceutical composition of the present invention might comprise proteinaceous carriers, like, e.g., serum albumine or immunoglobuline, preferably of human origin. It is envisaged that the pharmaceutical composition of the invention might comprise, in addition to the proteinaceous bispecific single chain antibody constructs or nucleic acid molecules or vectors encoding the same (as described in this invention), further biologically active agents, depending on the intended use of the pharmaceutical composition. Such agents might be drugs acting on the gastro-intestinal system, drugs acting as cytostatica, drugs preventing hyperurikemia, drugs inhibiting immunoreactions (e.g. corticosteroids), drugs acting on the circulatory system and/or agents such as T-cell co-stimulatory molecules or cytokines known in the art.

Possible indications for administration of the human binding molecule(s) of the invention are tumorous diseases, especially epithelial cancers/carcinomas such as breast cancer, colon cancer, prostate cancer, ovarian cancer or lung cancer or other tumorous diseases like haematological tumors, gliomas, sarcomas, osteosarcomas, head and neck cancer, skin cancer, cancers of the genitor-urinary tract, endometrial cancer, cervix cancer, kidney cancer, gastric cancer, cancer of the small intestine, liver cancer, pancreas cancer, gall bladder cancer, cancers of the bile duct, esophageal cancer, cancer of the salivatory glands or cancer of the thyroid gland. The administration of the human binding molecule(s) of the invention

of the invention is especially indicated for minimal residual disease, which is characterized by the local and non-local reoccurrance of the tumor caused by the survival of single cells. Further possible indications for administration of the constructs of the invention may comprise autoimmune diseases, especially T cell mediated autoimmune diseases, inflammatory diseases, infectious diseases, especially bacterial and fungal infections, viral diseases, allergic reactions, parasitic reactions, graft versus host disease, host versus graft disease, transplant rejection.

The invention further envisages co-administration protocols with other compounds, e.g. bispecific antibody constructs, targeted toxins or other compounds, which act via T cells. The clinical regimen for co-administration of the inventive compound(s) may encompass co-administration at the same time, before or after the administration of the other component.

The human binding molecule of the invention may also be modified or derivatized. Corresponding modifications may comprise the use of recombinant DNA technologies to improve the binding specificity, avidity, half life etc of the inventive human binding molecule.

A possible approach to demonstrate the efficacy/activity of the inventive constructs is an in vivo model. A suitable model may be a mouse model. Illustratively, such models may be chosen from mouse models expressing human CD3 and human EpCAM, chimeric mouse models expressing human CD3 and mouse models into which human tumors have been transplanted or tumor cells injected or chimeric mouse models into which human PBMCs have been injected. Preferred models for such assays are nude mice.

As detailed herein, the pharmaceutical composition of the invention may be administered to a patient in need of medical intervention (preferably a human patient). The pharmaceutical composition may administered alone or in combination with other medicaments/pharmaceutical compositions. These further medicaments/pharmaceutical compositions may be administered simultaneously or non-simultaneously with the pharmaceutical composition of the invention.

Alternatively the present invention relates in a preferred embodiment to a composition, which is a diagnostic composition further comprising, optionally, means and methods for detection.

A further alternative embodiment of the invention relates to the use of a human binding molecule of the invention or as produced by a process of the invention, a nucleic acid molecule of the invention, a vector of the invention or a host of the invention for the preparation of a pharmaceutical composition for the prevention, treatment or amelioration of a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, viral disease, allergic reactions, parasitic reactions, graft-versus-host diseases or host-versus-graft diseases.

In particular, the pharmaceutical composition of the present invention may be particularly useful in preventing, ameliorating and/or treating cancer, B-cell malignancies, acute myeloid leukaemia, chronic myeloid leukemia, leukemias, arthritis, asthma, allergies or other autoimmune disorders/diseases.
The term "immunological disorders" relates to autoimmune diseases, skin diseases, allergic diseases, inflammatory diseases, diabetes, transplant rejections and graft versus host disease, wherein said autoimmune disease is selected from the group consisting of type I diabetes and rheumatoid arthritis.
Said skin diseases, may comprise psoriatic lesions, psoriasis, atrophic dermatitis, atopic dermatitis, skin inflammation and the like. Inflammatory disease mentioned hereinabove is selected from the group consisting of inflammatory joint diseases, inflammatory renal diseases, inflammatory bowel diseases. In particular, said inflammatory bowel disease may comprise Morbus Crohn, sarcoidosis, systemic sclerosis, collagenosis, myositis, neuritis. Inflammatory renal diseases may comprise nephritis, glomerulonephritis, lupus nephritis, or IgA nephropathy and inflammatory joint disease may comprise (chronic) arthritis.
Said autoimmune disease is selected from the group consisting of Pemphigus vulgaris, Bullous pemphigoid, Goodpasture's syndrome, autoimmune haemolytic

anemia (AIHA), rheumatoid arthritis, Systemic Lupus erythematosus, Grave's disease (autoimmune hyperthyroidism), contact dermatitis, Myasthenia gravis, juvenile diabetes, Sjogren's syndrome, autoimmune thyroiditis, primary hypoadrenalism (Addison's disease), thrombocytopenic purpura, Morbus Wegener (granulomatosis), pemphigus foliaceous and celiac disease.

Autoimmune diseases are generally divided into three types: B-cell dominant, T-cell dominant or combinational types. Pathogenic phenotypes of B-cell dominant autoimmune diseases are caused by autoantibodies produced by autoreactive B-cells, while those of the T-cell dominant type are caused by tissue damage mediated by activated T-cells. These T-cells are activated by other cells presenting autoreactive peptide-MHC complexes on their surface. Yet, these distinctions are not perspicuous, since B-cells and T-cells cooperate with and depend on each other in each type of autoimmune disease. Autoimmune diseases are classified as combinatorial when both autoreactive B- and T-cells contribute directly to the pathogenesis observed ("Immunobiology", 4th edt. (1999), Chapter 13 pp 489-536, Janeway, C.A., Travers, P., Walport, M., Capra, J.D. eds and "Harrison's Principles in Internal Medicine" ,14th edt, Fauci, Braunwald, Isselbacher, Wilson, Martin, Kasper, Hauser, Longo, eds).

The pathogenic effects of autoreactive B cells are caused by the secreted autoreactive antibodies. Antibody-mediated autoimmune diseases can be differentiated into two major groups based on their immunopathogenic mechanism. The first group comprises autoimmune responses against cell-surface or extracellular matrix antigens, while the second group consists of immune-complex diseases.

Examples of the first group of antibody-mediated autoimmune diseases are autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, myasthenia gravis, Goodpasture's syndrome, immunologically mediated blistering diseases like Pemphigus vulgaris and pemphigus foliaceus, and acute rheumatic fever. Examples of the second group comprise mixed essential cryoglobulinemia, subacute bacterial endocarditis, and several rheumatic autoimmune diseases

Possible indications for administration of the human binding molecule of the

invention are tumorous diseases especially epithelial cancers/carcinomas such as mamma carcinoma, colon carcinoma, prostate carcinoma, ovarial carcinoma or lung carcinoma or other tumorous diseases like haematological tumors, glioma, sarcoma or osteosarcoma. Preferably, the constructs of the invention may be administered in non-small cell lung cancer, prostate cancer, adenocarcinoma, squamous and adenocarcinomas of the cervix, breast cancer, squamous cell carcinoma of the head and neck, small cell lung cancer, colorectal and pancreatic carcinoma or colon carcinoma.

Preferably said tumorous disease is epithelial cancer or a minimal residual cancer.

Indications for administration of pharmaceutical compositions of the invention providing to a subject a human binding molecules with specificity for the human CD3 complex and at least one further second target domain are exemplified in table 9.

Table 9: Indications for preferred second target domains

Preferred second target domains	Exemplified disorders/malignancies to be treated
CD19 (Kvalheim, Bone Marrow Transplant 1988, 3(1):31-41; Dörken, Lancet 1974 Dec 14;2(7894):1463)	Various B cell malignancies: Various B cell malignancies:
CD30 (Wahl, Cancer Res 2002, 62(13):3736-42)	Hodgkin lymphoma
CD33 (Maslak, Expert Opin Investig Drugs 2000, 9(6):1197-205; Stadtmauer, Curr Oncol Rep 2002, 4(5):375-80)	AML (acute myeloic leukemia)
CD33 (Lopez-Karpovitch, Rev Invest Clin 1997, 49(1):31-6)	CML (chronic myeloic leukemia)
CD25 (Dahmoush, Cancer 2002, 96(2):110-6; Savoie, Curr Treat Options Oncol 2001, 2(3):217-24)	Certain T-cell and B-cell leukemias
CD19 (Issacs, Arthritis Rheum 2001, 44(9):1998-2008), **CCR5** (Bruhl, J Immunol 2001, 166(4):2420-6), **TNF-alpha precursor** (Wollheim, Expert Opin Investig	Rheumatoid arthritis

Drugs 2002, 11(7):947-53)	
CD19 (Sato, J Immunol 2000, 165(11):6635-43, **CCR5** (Zapico, Genes Immun 2000;1(4):288-9), **CD30** (Okumura, J Clin Endocrinol Metab 1997, 82(6):1757-60)	Autoimmune diseases
CCR8 (Owen, Pulm Pharmacol Ther 2001;14(3):193-202)	Asthma
IgE (membrane bound) (Lustgarten, Eur J Immunol 1995, 25(10):2985-91)	Allergy
EpCAM (Naundorf, Int J Cancer 2002, 100(1):101-10), **EGFR** (Liu, Br J Cancer 2000, 82(12):1991-9), **CEA** (Stewart, Cancer Immunol Immunother 1999, 47(6):299-306 ; Durbin, Proc Natl Acad Sci U S A 1994,91(10):4313-7), **TAG-72** (tumor associated glycoprotein =>sTn antigen) (Kashmiri, Crit Rev Oncol Hematol 2001, 38(1):3-16), **Sonic Hedgehog** (Shh) (Lacour, Br J Dermatol 2002, 146 Suppl 61:17-9 ; Tojo, Br J Dermatol 2002, 146(1):69-73)	Pan-carcinoma
Her-2 (Arteaga, Semin Oncol 2002, 29(3 Suppl 11):4-10; Wester, Acta Oncol 2002;41(3):282-8)	Mamma carcinoma and other carcinomas
EGFR (Bonner, Semin Radiat Oncol 2002, 12 : 11-20 ; Kiyota, Oncology 2002; 63 (1) : 92-8) , **CD44v6 related to stage of carcinoma** (Rodrigo, Am J Clin Pathol 2002, 118(1):67-72; Fonseca, J Surg Oncol 2001, 76(2):115-20)	Squamous cell carcinoma
PSMA (Fracasso, Prostate 2002, 53(1):9-23), **STEAP** (Hubert, Proc Natl Acad Sci U S A 1999, 96(25):14523-8), **PSCA** (prostate stem cell antigen) (Jalkut, Curr Opin Urol 2002, 12(5):401-6)	Prostate cancer
CEA (Stewart, Cancer Immunol Immunother 1999, 47(6):299-306 ; Durbin, Proc Natl Acad Sci U S A 1994, 91(10):4313-7), **TAG-72** (tumor associated glycoprotein =>sTn antigen) (Kashmiri, Crit Rev Oncol Hematol 2001, 38(1):3-16),	Adenocarcinoma
MUC-1 (mucin) (Couto, Adv Exp Med Biol 1994;353:55-9)	Breast cancer
ganglioside GD3 (Brezicka, Lung Cancer 2000, 28(1):29-36; Sheperd, Semin Oncol	SCLC (small cell lung cancer)

2001, 28(2 Suppl 4):30-7)	
mesothelin (Scholler, Proc Natl Acad Sci U S A 1999, 96(20):11531-6; Brinkmann, Int J Cancer 1997, 71(4):638-44), **CA-125** (Hogdall, Anticancer Res 2002, 22(3):1765-8), **Muellerian Inhibitory Substance (MIS) Receptor Type II** (Stephen, Clin Cancer Res 2002, 8(8):2640-6)	Ovarian cancer
Ly-6 (Eshel, Int J Cancer 2002, 98(6):803-10), **desmoglein 4** (Tomson, Clin Exp Metastasis 1996, 14(6):501-11)	Head and Neck cancer
Lewis-Y (Power, Cancer Immunol Immunother 2001, 50(5):241-50)	Epithelial cancers
E-cadherin neoepitope (Becker, Surg Oncol 2000, 9(1):5-11)	Gastric cancers
MUC-1 (mucin) (Hanski, Cancer Res 1993, 53(17):4082-8), **Lewis-Y** (Flieger, Clin Exp Immunol 2001, 123(1):9-14; Power, Cancer Immunol Immunother 2001, 50(5):241-50), **A33 antigen** (Heath, Proc Natl Acad Sci U S A 1997, 94(2):469-74)	Colon carcinoma
Carbonic anhydrase IX (MN/CA IX) (Uemura, Br J Cancer 1999, 81(4):741-6	Renal cell carcinoma
Carbonic anhydrase IX (MN/CA IX) (Longcaster, Cancer Res 2001, 61(17):6394-9)	Cervix carcinoma
Carbonic anhydrase IX (MN/CA IX) (Chia, J Clin Oncol 2001, 19(16):3660-8)	Breast carcinoma
Carbonic anhydrase IX (MN/CA IX) (Beasley, Cancer Res 2001, 61(13):5262-7)	Head and neck squamous cell carcinoma
CA19-9 marker (Brockmann, Anticancer Res 2000, 20(6D):4941-7)	Pancreas carcinoma
Fetal AchR (acetylcholine receptor) (Gattenloehner, Am J Pathol 1998, 152(2):437-44)	Rhabdomyosarcoma
EGFR (Kuan, Brain Tumor Pathol 2000;17(2):71-8)	Glioma
Wue-1 Plasma cell antigen (Greiner, Virchows Arch 2000, 437(4):372-9)	Multiple Myeloma
ganglioside GD3 (Dippold, Cancer Res 1984, 44(2):806-10; Scott, J Clin Oncol 2001,19(19):3976-87), **MCSP** (melanoma	Melanoma

chondroitin sulfate proteoglycan) (Pluschke, Proc Natl Acad Sci U S A 1996, 93(18):9710-5; Geiser, Cancer Res 1999, 59(4):905-10)	
CD44v6 (Rodrigo, Am J Clin Pathol 2002, 118(1):67-72; Fonseca, J Surg Oncol 2001, 76(2):115-20)	Metastatic disease
CD20 (Chu, 2002, Leuk. Lymphoma 43, 23335-23337)	Non-Hodgkin's lymphoma

It is envisaged by the present invention that the human binding molecules, nucleic acid molecules and vectors of the invention are administered either alone or in any combination using standard vectors and/or gene delivery systems, and optionally together with a pharmaceutically acceptable carrier or excipient. Subsequent to administration, said nucleic acid molecules or vectors may be stably integrated into the genome of the subject.

On the other hand, viral vectors may be used which are specific for certain cells or tissues and persist in said cells. Suitable pharmaceutical carriers and excipients are well known in the art. The pharmaceutical compositions prepared according to the invention can be used for the prevention or treatment or delaying the above identified diseases.

Furthermore, it is possible to use a pharmaceutical composition of the invention which comprises nucleic acid molecules or vectors of the invention in gene therapy. Suitable gene delivery systems may include liposomes, receptor-mediated delivery systems, naked DNA, and viral vectors such as herpes viruses, retroviruses, adenoviruses, and adeno-associated viruses, among others. Delivery of nucleic acids to a specific site in the body for gene therapy may also be accomplished using a biolistic delivery system, such as that described by Williams (Proc. Natl. Acad. Sci. USA 88 (1991), 2726-2729). Further methods for the delivery of nucleic acids comprise particle-mediated gene transfer as, e.g., described in Verma, Gene Ther.15 (1998), 692-699.

Furthermore the invention relates to a method for the prevention, treatment or amelioration of a proliferative disease, a tumorous disease, an inflammatory

disease, an immunological disorder, an autoimmune disease, an infectious disease, viral disease, allergic reactions, parasitic reactions, graft-versus-host diseases or host-versus-graft diseases in a subject in the need thereof, said method comprising the step of administration of an effective amount of a human binding molecule of the invention or as produced by a process of the invention, a nucleic acid molecule of the invention, a vector of the invention or a host of the invention.

Preferably said subject is a human.

The method for the prevention, treatment or amelioration of the invention may comprise the co-administration of an above defined proteinaceous compound capable of an activation signal for immune effector cells to the subject. The co-administration may be a simultaneous co-administration or a non-simultaneous co-administration.

Finally, the present invention relates to a kit comprising a human binding molecule of the invention or as produced by a process of the invention, a nucleic acid molecule of the invention, a vector of the invention or a host of the invention. It is also envisaged that the kit of this invention comprises a pharmaceutical composition as described herein above, either alone or in combination with further medicaments to be administered to a patient in need of medical treatment or intervention.

The Figures show:

Throughout the following figure legends as well as the appended examples, the abbreviation "Hu" shall denote "Human".

Fig. 1: DNA and protein sequences of the mouse C kappa domain with a C-terminally attached His6-tag. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The relevant restriction sites for cloning this DNA-fragment into a translational fusion protein with scFvs are shown (BsiWI, NotI).

Fig. 2: CD3-specific ELISA-analysis of periplasmic preparations containing scFv protein fragments from the selection of huLIB-ST (phage pool 1). Periplasmic preparations of soluble scFv protein fragments were added to wells of an ELISA-plate, which had been coated with a soluble recombinant CD3-epsilon antigen. Detection of scFv-fragments bound to immobilized recombinant human CD3 epsilon antigen was carried out using a biotinylated anti-mouse kappa antibody (Southern Biotech, 1µg/ml PBS) detected with horseradish peroxidase-conjugated avidine (Dako, 1µg/ml PBS). The ELISA was developed by an ABTS (2,2'-Azino-di[3-ethylbenzthiazoline sulfonate (6)] diammonium salt)-substrate solution as described in Example 3. The OD-values (y axis) were measured at 405 nm by an ELISA reader. Clone numbers are presented on the x axis, where the first number of the clone number indicates the round of panning in which the respective clone was obtained, while the second number indicates the respective clone of this round.

Fig. 3: CD3-specific ELISA-analysis of periplasmic preparations containing scFv protein fragments from the selection of huLIB-ST (phage pool 2). Periplasmic preparations of soluble scFv protein fragments were added to wells of an ELISA-plate that had been coated with soluble recombinant CD3-epsilon antigen. Detection of scFv-fragments bound to immobilized recombinant human CD3 epsilon antigen was carried out using a biotinylated anti-mouse kappa antibody (Southern Biotech, 1µg/ml PBS) detected with horseradish peroxidase-conjugated avidine (Dako, 1µg/ml PBS). The ELISA was developed by an ABTS-substrate solution as described in example 3. The OD-values (Y-axis) were measured at 405 nm by an ELISA-reader. Clone numbers are presented on the X-axis, where the first number of the clone number indicates the round of panning in which the respective clone was obtained, while the second number indicates the respective clone of this round.

Fig. 4: CD3-specific ELISA-analysis of periplasmic preparations containing scFv

protein fragments from the selection of huLIB-STE (phage pool 3). Periplasmic preparations of soluble scFv protein fragments were added to wells of an ELISA-plate that had been coated with soluble recombinant CD3-epsilon antigen. Detection of scFv-fragments bound to immobilized recombinant human CD3 epsilon antigen was carried out using a biotinylated anti-mouse kappa antibody (Southern Biotech, 1µg/ml PBS) detected with horseradish peroxidase-conjugated avidine (Dako, 1µg/ml PBS). The ELISA was developed by an ABTS-substrate solution as described in Example 3. The OD-values (Y-axis) were measured at 405 nm by an ELISA-reader. Clone numbers are presented on the X-axis, where the first number of the clone number indicates the round of panning in which the respective clone was obtained, while the second number indicates the respective clone of this round.

Fig. 5: CD3-specific ELISA-analysis of periplasmic preparations containing scFv protein fragments from the selection of huLIB-STE (phage pool 4). Periplasmic preparations of soluble scFv protein fragments were added to wells of an ELISA-plate that had been coated with soluble recombinant CD3-epsilon antigen. Detection of scFv-fragments bound to immobilized recombinant human CD3 epsilon antigen was carried out using an anti-Flag-tag antibody (M2 Sigma 1µg/ml PBS) detected with horseradish peroxidase-conjugated polyclonal anti-mouse antibody (Dako 1µg/ml PBS). The ELISA was developed by an ABTS-substrate solution as described in Example 3. The OD-values (Y-axis) were measured at 405 nm by an ELISA-reader. Clone numbers are presented on the X-axis, where the first number of the clone number indicates the round of panning in which the respective clone was obtained, while the second number indicates the respective clone of this round.

Fig. 6: DNA and protein sequences of the human scFv fragment 3-106. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 375 followed by a $(G_4S_1)_3$-linker. The coding region of

the DNA sequence for the V-region of the kappa (light) chain starts at nt 421 and ends at nt 741. Complementarity determining regions (CDRs) are indicated by boxes surrounding the relevant nt and aa positions (according to the Kabat definition for CDRs).

Fig. 7: DNA and protein sequences of the human scFv fragment 3-114. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 366 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 412 and ends at nt 732. Complementarity determining regions (CDRs) are indicated by boxes surrounding the relevant nt and aa positions (according to the Kabat definition for CDRs).

Fig. 8: DNA and protein sequences of the human scFv fragment 3-148. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 360 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 406 and ends at nt 726. Complementarity determining regions (CDRs) are indicated by boxes surrounding the relevant nt and aa positions (according to the Kabat definition for CDRs).

Fig. 9: DNA and protein sequences of the human scFv fragment 3-190. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 378 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 424 and ends at nt 744. Complementarity determining regions (CDRs) are indicated by boxes surrounding the relevant nt and aa positions (according to the Kabat definition for CDRs).

Fig. 10: DNA and protein sequences of the human scFv fragment 3-271. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 357 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 403 and ends at nt 723. Complementarity determining regions (CDRs) are indicated by boxes surrounding the relevant nt and aa positions (according to the Kabat definition for CDRs).

Fig. 11: DNA and protein sequences of the human scFv fragment 3-550. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 381 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 427 and ends at nt 750. Complementarity determining regions (CDRs) are indicated by boxes surrounding the relevant nt and aa positions (according to the Kabat definition for CDRs).

Fig. 12: DNA and protein sequence of the human scFv fragment 4-10. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 363 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 409 and ends at nt 729. Complementarity determining regions (CDRs) are indicated by boxes surrounding the relevant nt and aa positions (according to the Kabat definition for CDRs).

Fig. 13: DNA and protein sequence of the human scFv fragment 4-48. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain

starts at nt 1 and ends at nt 369 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 415 and ends at nt 753. Complementarity determining regions (CDRs) are indicated by boxes surrounding the relevant nt and aa positions (according to the Kabat definition for CDRs).

Fig. 14: CD3-specific ELISA-analysis of periplasmic preparations containing Flag-tagged scFv protein fragments from selected clones. Periplasmic preparations of soluble scFv protein fragments were added to wells of an ELISA-plate, which had been coated with soluble recombinant CD3-epsilon antigen and had been additionally blocked with PBS 3 % BSA. Detection was performed by a monoclonal anti-Flag antibody followed by a peroxidase-conjugated polyclonal goat anti-mouse antibody. The ELISA was developed by an ABTS-substrate solution as described in Example 3. The OD-values (Y-axis) were measured at 405 nm by an ELISA-reader. Clone numbers are presented on the X-axis, where the first number of the clone number indicates the round of panning in which the respective clone was obtained, while the second number indicates the respective clone of this round. Periplasmic preparation from cells producing the anti-CD3 scFv L2K was included, as well as the purified anti-CD3 antibodies UCHT1, SP34 and OKT3 (concentration of each 1 µg/ml).

Fig. 15: ELISA-analysis of periplasmic preparations containing Flag-tagged scFv protein fragments from selected clones. The same periplasmic preparations of soluble scFv protein fragments as in Fig. 14 were added to wells of an ELISA-plate that had not been coated with soluble recombinant CD3-epsilon antigen but rather only blocked with PBS 3 % BSA. Detection was performed by a monoclonal anti-Flag antibody followed by a peroxidase-conjugated polyclonal goat anti-mouse antibody. The ELISA was developed by an ABTS-substrate solution as described in example 3. The OD-values (Y-axis) were measured at 405 nm by an ELISA-reader. Clone numbers are presented on the X-axis, where the first number of the clone number indicates the round of panning in which the respective clone was

obtained, while the second number indicates the respective clone of this round. Periplasmic preparation from cells producing the anti-CD3 scFv L2K was included, as well as the purified anti-CD3 antibodies UCHT1, SP34 and OKT3 (concentration of each 1 µg/ml).

Fig. 16: Flow cytometric analysis of periplasmic preparations containing Flag-tagged scFv protein fragments from selected clones (4-10, 4-48, 3-550, 3-106, 3-114, 3-148, 3-190, 3-271). Periplasmic preparations of soluble scFv protein fragments were added to CD3-positive Jurkat cells. Detection was performed by a monoclonal anti-Flag antibody followed by a PE-labeled polyclonal anti-mouse antibody. ScFvs binding to cells was measured by an increase in fluorescence intensity as compared to cells that were incubated with PBS alone. Fluorescence intensity is blotted on the X-axis, the number of events is blotted on the Y-axis. The negative control is shown in black, the respective scFvs are shown in gray. Shifting to the right indicates positive binding to the cells. Periplasmic preparation from cells producing the anti-CD3 scFv L2K was included, as well as the purified anti-CD3 antibodies UCHT1, SP34 and OKT3 (concentration of each 5 µg/ml).

Fig. 17: Flow cytometric analysis of periplasmic preparations containing Flag-tagged scFv protein fragments from selected clones (3-106, 3-114, 3-148, 3-190, 3-271, 3-550, 4-10, 4-48). Periplasmic preparations of soluble scFv protein fragments were added to CD3-negative CHO cells. Detection was performed by a monoclonal anti-Flag antibody followed by a PE-labeled polyclonal anti-mouse antibody. Binding of scFv constructs to cells was measured by an increase in fluorescence intensity as compared to cells that were incubated with PBS alone. Fluorescence intensity is blotted on the X-axis, the number of events is blotted on the Y-axis. The negative control is shown in black, the respective scFvs are shown in gray. Shifting to the right indicates positive binding to the cells. Periplasmic preparation from cells producing the anti-CD3 scFv L2K was included, as well as the purified anti-CD3 antibodies UCHT1, SP34 and OKT3 (concentration of each 5 µg/ml).

Fig. 18: Flow cytometric analysis of periplasmic preparations containing Flag-tagged scFv protein fragments from selected clones (3-106, 3-114, 3-148, 3-190, 3-271, 3-550, 4-10, 4-48). Periplasmic preparations of soluble scFv protein fragments were added to CD3-negative KatoIII cells. Detection was performed by a monoclonal anti-Flag antibody followed by a PE-labeled polyclonal anti-mouse antibody. Binding of scFv constructs to cells was measured by an increase in fluorescence intensity as compared to cells that were incubated with PBS alone. Fluorescence intensity is blotted on the X-axis, the number of events is blotted on the Y-axis. The negative control is shown in black, the respective scFvs are shown in gray. Shifting to the right indicates positive binding to the cells. Periplasmic preparation from cells producing the anti-CD3 scFv L2K was included, as well as the purified anti-CD3 antibodies UCHT1, SP34 and OKT3 (concentration of each 5 µg/ml).

Fig. 19: Flow cytometric analysis of periplasmic preparations containing Flag-tagged 3-271 scFv protein fragments from selected clones. Periplasmic preparation of soluble 3-271 scFv protein fragments was added to CD3-positive Jurkat cells. Detection was performed by a monoclonal anti-Flag antibody followed by a PE-labeled polyclonal anti-mouse antibody. Binding of scFv constructs to cells was measured by an increase in fluorescence intensity as compared to cells that were incubated with PBS alone. Fluorescence intensity is blotted on the X-axis, the number of events is blotted on the Y-axis. The negative control is shown in black, the respective scFvs are shown in gray. Shifting to the right indicates positive binding to the cells. Periplasmic preparation from cells producing the anti-CD3 scFv L2K was included, as well as the purified anti-CD3 antibodies UCHT1, SP34 and OKT3 (concentrations of each 5 µg/ml).

Fig. 20: Flow cytometric analysis of periplasmic preparations containing Flag-tagged 3-271 scFv protein fragments from selected clones. Periplasmic preparations of soluble 3-271 scFv protein fragments was added to CD3-negative

CHO cells. Detection was performed by a monoclonal anti-Flag antibody followed by a PE-labeled polyclonal anti-mouse antibody. ScFvs binding to cells was measured by an increase in fluorescence intensity as compared to cells that were incubated with PBS alone. Fluorescence intensity is blotted on the X-axis, the number of events is blotted on the Y-axis. The negative control is shown in black, the respective scFvs are shown in grey. Shifting to the right indicated positive binding to the cells. Periplasmic preparation from cells producing the anti-CD3 scFv L2K was included, as well as the purified anti-CD3 antibodies UCHT1, SP34 and OKT3 (concentration of each 5 µg/ml).

Fig. 21: Flow cytometric analysis of periplasmic preparations containing Flag-tagged 3-271 scFv protein fragments from selected clones. Periplasmic preparation of soluble 3-271 scFv protein fragments was added to CD3-epsilon and –gamma cotransfected CHO cells. Detection was performed by a monoclonal anti-Flag antibody followed by a PE-labeled polyclonal anti-mouse antibody. ScFvs binding to cells were measured by an increase in fluorescence intensity as compared to cells that were incubated with PBS alone. Fluorescence intensity is blotted on the X-axis, the number of events is blotted on the Y-axis. The negative control is shown in black, the respective scFvs are shown in grey. Shifting to the right indicates positive binding to the cells. Periplasmic preparation from cells producing the anti-CD3 scFv L2K was included, as well as the purified anti-CD3 antibodies UCHT1, SP34 and OKT3 (concentration of each 5 µg/ml).

Fig. 22: DNA and protein sequences of the anti-EpCAM scFv fragment 5-10. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 360 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 406 and ends at nt 744.

Fig. 23: DNA and protein sequences of the anti-CD19 scFv fragment. Numbers

indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 372 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 418 and ends at nt 750.

Fig. 24: DNA and protein sequences of the anti-CD20 scFv fragment. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 366 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 412 and ends at nt 729.

Fig. 25: DNA and protein sequences of the anti-CCR5 scFv fragment. Numbers indicate the nucleotide (nt) positions, amino acids (aa) are presented in single letter code. The coding region of the DNA sequence for the V-region of the heavy chain starts at nt 1 and ends at nt 354 followed by a $(G_4S_1)_3$-linker. The coding region of the DNA sequence for the V-region of the kappa (light) chain starts at nt 399 and ends at nt 732.

Fig. 26: Cytotoxic activity of the bispecific antibody biscFv anti-CD3 3-190 x anti-CD19 as measured by fluorochrome release. Purified bispecific scFv ("biscFv") 3-190 x anti-CD19 P2 (protein fraction 2 from gel filtration) was evaluated using CD19 positive fluorochrome-labeled NALM6 cells as target cells and CD3-positive CB15 T cells as effector cells (E:T ratio of 1:10). biscFv 3-190 x anti-CD19 P2 was diluted in RPMI/10% FCS in a dilution series and 50 µl of the respective solution were added to the cell suspension. The same dilution series was performed using PBS as negative control, starting with the same volume as for biscFv 3-190 x anti-CD19 P2. After lysis of target cells, the dye released into the incubation medium was quantitated in a fluorescence reader and compared with the fluorescence signal from a control reaction (without bispecific antibody), and the fluorescence

signal was obtained for totally lysed cells. Specific cytotoxicity was calculated according to the following formula: [Fluorescence (Sample) - Fluorescence (Control)] : [Fluorescence (Total Lysis)- Fluorescence (Control)] x 100, wherein ":" denotes mathematical division. Concentrations are plotted on the X-axis, % specific toxicity on the Y-axis.

Fig. 27: Cytotoxic activity of the bispecific antibodies anti-CD3 3-271 x 5-10 anti-EpCAM, 5-10 anti-EpCAM x anti-CD3 3-148 and 5-10 anti-EpCAM x anti-CD3 3-190 measured by fluorochrome release. For this experiment anti-CD3 3-271 x 5-10 anti-EpCAM P2 (protein fraction 2 from gel filtration), anti-CD3 3-271 x 5-10 anti-EpCAM P3 (protein fraction 3 from gelfiltration), 5-10 anti-EpCAM x anti-CD3 3-148 (main protein fraction from gelfiltration) and 5-10 anti-EpCAM x anti-CD3 3-190 P3 (protein fraction 3 from gelfiltration) were used with EpCAM-transfected CHO and non-transfected cells as target cells and CD3-positive CB15 T cells as effector cells (E:T ratio of 1:5). Anti-CD3 3-190 x anti-CD19 P2 (protein fraction 2 from gelfiltration) was included as an appropriate negative control for CD19-negative CHO-EpCAM cells. M79, an anti-EpCAM x anti-CD3 biscFv construct was used as a positive control. Untransfected CHO as well as CHO-EpCAM were labeled with PKH26. Antibody constructs were diluted in RPMI/10% FCS and added to the cell suspension. After 16 h propidium iodide (PI) was added and the cells were analyzed by flow cytometry. Cytotoxicity was measured as the ratio of PI positive cells over all target cells. The biscFv constructs are plotted on the X-axis according to the respective concentrations used for each construct, and the % specific cytotoxicity is plotted on the Y-axis.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of scope of the present invention.

Example 1: Procurement of the extracellular domain of the human CD3-epsilon chain for use as selection antigen in phage display

1.1. Cloning of the extracellular domain of the human CD3 epsilon chain:

cDNA was isolated from human peripheral blood mononuclear cells. Preparation of the cells was performed according to standard protocols (Current Protocols in Immunology (Coligan, Kruisbeek, Margulies, Shevach and Strober, John Wiley & Sons, Inc., USA, 2002)). The isolation of total RNA and cDNA synthesis by random-primed reverse transcription was performed according to standard protocols (Sambrock, Molecular Cloning; Laboratory Manual, 2nd edition, Cold Spring Harbor laboratory Press, Cold Spring Harbor, New York (1989)). PCR was used to amplify the coding sequence of the extracellular domain of the human CD3 epsilon chain. The primers used in the PCR were designed so as to introduce restriction sites at the beginning and the end of the cDNA coding for the extracellular portion of the human CD3 epsilon chain (SEQ ID NO: 137 and SEQ ID NO:138). The introduced restriction sites, BsrGI and BspEI, were utilised in the following cloning procedures. The PCR product was then cloned via BsrGI and BspEI into a plasmid designated BS-Fss-Lsp derived from the Bluescript KS^+ cloning vector (Stratagene Europe, Amsterdam-Zuiddoost, the Netherlands) following standard protocols. (The vector was generated by cloning a DNA fragment (SEQ ID NO: 139) via EcoRI and SalI into Bluescript KS^+.) The sequence of different clones was determined by sequencing according to standard protocols. By cloning into BS-Fss-Lsp the coding sequence of a murine immunoglobulin heavy chain leader peptide was fused in-frame to the 5' end of the coding sequence for the extracellular portion of the human CD3 epsilon chain. The cDNA was then cloned via EcoRI and BspEI into another plasmid designated as BSCTI to attach a sequence to the C-terminus, coding for a polyhistidine tag of six consecutive histidine residues followed by a stop codon (BSCTI is described in Kufer, Cancer Immunity 1 (2001), 10). In this step the BspEI site of the cDNA was fused into an XmaI site of the plasmid thereby destroying both sites. All cloning steps were designed so as to generate an intact reading frame for the construct. The plasmid now contained a sequence coding for a protein comprising a murine immunoglobulin heavy chain leader peptide, to allow for secreted expression,

followed by the extracellular domain of the human CD3 epsilon chain followed by a polyhistidine tag of six consecutive histidine residues, to allow for purification and detection via the polyhistidine tag (SEQ ID NO: 140 and SEQ ID NO: 141). This sequence was then cloned into the plasmid pFastBac1™ (Invitrogen GmbH, Karlsruhe, FRG) via EcoRI and SalI.

1.2. Expression of the extracellular domain of the human CD3 epsilon chain in High Five™ cells, purification of the recombinant protein

Expression of the extracellular domain of the human CD3 epsilon chain in High Five™ cells was performed using the *Bac-to-Bac® Baculovirus Expression System* (Invitrogen GmbH, Karlsruhe, FRG) according to the specifications of the manufacturer. 10 litres of supernatant in batches of 500 ml were produced. The construct was then purified out of the culture supernatant. Purification was performed as a two-step purification. First the diluted supernatants were loaded on ion exchange columns. The fractionated eluate was tested in an ELISA assay. To this end, an anti-human CD3 epsilon antibody (UCHT1 BD biosciences, Heidelberg, FRG) was coated (50 µl at 5 µg/ml in PBS) on a Maxisorp ELISA plate (Nunc GmbH, Wiesbaden, FRG) overnight. Unspecific binding was blocked with 1.5 % BSA in PBS for 1 hour. All prior and subsequent washing steps were performed three times with 200 µl PBS. Afterwards, eluate fractions were incubated for 1 hour in the prepared cavities of the plate. Detection of the recombinant protein was performed with a horseradish peroxidase conjugated anti-His antibody (Roche Diagnostics GmbH, Mannheim, FRG; 50 µl of antibody diluted 1:500 in 1.5 % BSA in PBS). Development of the ELISA was performed with ABTS (2,2'-Azino-bis(3-Ethylbenz-Thiazolin)-6-Sulfonic acid) Roche Diagnostics GmbH, Mannheim, FRG) according to the specifications of the manufacturer. Positive fractions were further purified over a cobalt-chelate column which preferentially binds histidine-tagged proteins. Eluate fractions were tested using the described ELISA assay. Positive fractions were pooled and concentrated.

Example 2: Construction of the combinatorial antibody library and phage display

2.1. Isolation of RNA from selected IgD-positive B-cells

100 ml blood were taken from five healthy human donors. Peripheral blood mononuclear cells (PBMCs) were isolated by a ficoll-gradient according to standard methods. To select IgD-positive cells, 1 ml anti-mouse IgG-beads (CELLection™ Pan Mouse IgG Kit; DYNAL) were coated with 20 µg mouse anti-human IgD-antibody (PharMingen). Approximately 2.5 x 10^7 PBMCs were added to the beads and incubated at 4°C for 15 minutes. After washing four times with 1 ml RPMI-medium (BioChrom) IgD-positive cells were released from the beads by adding 8 µl release buffer (DNase) and transferred to a fresh tube. By this method 0.9 x 10^5 to 3.7 x 10^6 IgD-positive cells could be obtained. Total RNA was isolated from IgD-positive cells using the RNeasy® Midi Kit (QIAGEN) following the manufacturers instructions. cDNA was synthesized according to standard methods (Sambrook, Cold Spring Harbor Laboratory Press 1989, Second Edition).

2.2. Isolation of RNA from PBMCs

100 ml blood from five healthy donors were taken, PBMCs were separated using a ficoll-gradient and total RNA was isolated from approximately 2.5 x 10^7 cells with the RNeasy® Midi Kit (QIAGEN) following the manufactures instructions. cDNA was synthesized according to standard methods (Sambrook, Cold Spring Harbor Laboratory Press 1989, Second Edition).

2.3. PCR-Amplification of variable regions (V-regions)

For the isolation of light chain V-region DNA, RT-PCR was carried out using V-kappa- (5'-huVK1-Sac-2001 (SEQ ID NO: 150), 5'-huVK2/4-Sac-2001 (SEQ ID NO: 152), 5'-huVK3-Sac-2001 (SEQ ID NO: 151), 5'-huVK5-Sac-2001 (SEQ ID NO: 153), 5'-huVK6-Sac-2001 (SEQ ID NO: 154), 3'-hu-Vk-J1-SpeI-BsiWI (SEQ ID NO: 155), 3'-hu-Vk-J2/4-SpeI-BsiWI (SEQ ID NO: 156), 3'-hu-Vk-J3-SpeI-BsiWI (SEQ ID NO: 157), 3'-hu-Vk-J5-SpeI-BsiWI (SEQ ID NO: 158) and V-lambda-specific (5'-huVL1a-SacI-2001 (SEQ ID NO: 159), 5'-huVL1b-SacI-2001 (SEQ ID NO: 160), 5'-huVL2-SacI-2001 (SEQ ID NO: 161), 5'-huVL4-SacI-2001 (SEQ ID NO: 162), 5'-huVL5-SacI-2001 (SEQ ID NO: 163), 5'-huVL6-SacI-2001 (SEQ ID

NO: 164), 5'-huVL3/9-SacI-2001 (SEQ ID NO: 165), 5'-huVL7/8-SacI-2001 (SEQ ID NO: 166), 3'-hu-Vlam-BlnI-SpeI-2001 (SEQ ID NO: 167), 3'-hu-Vlam2-BlnI-SpeI-2002 (SEQ ID NO: 168) primer sets. RNA from IgD positive B-cells was transcribed into cDNA (as described before) and used as template DNA in PCR reactions. Per PCR reaction, one 5'-primer was combined with one 3'-primer, wherein the 5'-kappa primer was combined with the 3'-kappa primer and the 5'-lambda primer was combined with the 3'-lambda primer. The number of different PCR reactions was determined by the number of possible combinations of 5'- and 3'-primers. The following PCR-program was used for amplification:

Denaturation at 94°C for 15 seconds, primer annealing at 52°C for 50 seconds and primer extension at 72°C for 90 seconds were performed over 40 cycles, followed by final extension at 72°C for 10 minutes. Light chain DNA V-fragments were then isolated according to standard protocols.

For the isolation of VH-regions, RT-PCR was carried out in two steps. First, the heavy chain Fd-fragments of IgD were PCR-amplified using a 5'-VH-specific primer set (5'-huVH1,3,5-XhoI-2001 (SEQ ID NO: 142), 5'-huVH2-XhoI-2001 (SEQ ID NO: 143), 5'-huVH4-XhoI-2001 (SEQ ID NO: 144), 5'-huVH4B-XhoI-2001 (SEQ ID NO: 145), 5'-huVH6-XhoI-2001 (SEQ ID NO: 146)) and a 3'-specific IgD-primer (3'-CD1 (SEQ ID NO: 147)). cDNA transcribed from RNA isolated from unselected PBMCs (as described before) was used as template. Per PCR reaction, one 5'-primer was combined with the 3'-primer; the number of different PCR reactions was determined by the number of possible combinations of 5'- and the 3'-primer. The following PCR-programm was used for amplification: Denaturation at 94°C for 15 seconds, primer annealing at 52°C for 50 seconds and primer extension at 72°C for 90 seconds was performed over 40 cycles, followed by final extension at 72°C for 10 minutes.

These IgD-Fd DNA-fragments were then used as templates in a second PCR reaction using again the 5'VH-specific primer set and a set of two 3'-VH-specific primers (3'-hu-VH-BstEII-2001 (SEQ ID NO: 148), 3'-hu-VH-J3-BstEII-2001 (SEQ ID NO: 149)). Per PCR reaction, one 5'-primer was combined with one 3'-primer; the number of different PCR reactions was determined by the number of possible

combinations of 5'- and 3'-primers.

The following PCR-program was used for the second step: Denaturation at 94°C for 15 seconds, primer annealing at 52°C for 50 seconds and primer extension at 72°C for 90 seconds was performed over 40 cycles, followed by final extension at 72°C for 10 minutes. Heavy chain DNA-fragments were then isolated according to standard protocols.

2.4. Library construction

A phage display library was generally constructed based on standard procedures, as for example disclosed in "Phage Display: A Laboratory Manual"; Ed. Barbas, Burton, Scott & Silverman; Cold Spring Harbor Laboratory Press, 2001.

The primers chosen for PCR amplification gave rise to a 5'- XhoI and a 3'-BstEII recognition site for the heavy chain V-fragments and to a 5'-SacI and a 3'- SpeI recognition site for light chain V-fragments.

In two parallel reactions each 400 ng of the kappa light chain fragments (SacI-SpeI digested) were ligated with 1400 ng of the phagemid pComb3H5BHis (SacI-SpeI digested; large fragment, vector described in WO 99/25818). The two resulting antibody V-light chain libraries were then each transformed into 300 µl of electrocompetent Escherichia coli XL1 Blue by electroporation (2.5 kV, 0.2 cm gap cuvette, 25 FD, 200 Ohm, Biorad gene-pulser) resulting in a library size of 1.8 x 10^8 independent clones in total.

Kappa (light chain) DNA-fragments from the different PCR amplifications were weighted for each ligation as follows: Each 5'-primer defines a specific group. Within these groups the 3'-primers define the subgroups. The subgroups were weighted 1:2:1:1 corresponding to the primers 3'-hu-Vk-J1-SpeI-BsiWI : 3'-hu-Vk-J2/4-SpeI-BsiWI : 3'-hu-Vk-J3-SpeI-BsiWI : 3'-hu-Vk-J5-SpeI-BsiWI . The groups were weighted according to their germline distribution 1:1:1:0.2:0.2 corresponding to the primers 5'-huVK1-Sac-2001 : 5'-huVK3-Sac-2001 : 5'-huVK2/4-Sac-2001 : 5'-huVK5-Sac-2001 : 5'-huVK6-Sac-2001.

As described for the kappa DNA fragments, two parallel ligation reactions were carried out, each containing 400 ng of the lambda light chain fragments (SacI-SpeI

digested) and 1400 ng of the phagemid pComb3H5BHis (SacI-SpeI digested). The two resulting antibody V-light chain libraries were then each transformed into 300 µl of electrocompetent Escherichia coli XL1 Blue by electroporation (2.5 kV, 0.2 cm gap cuvette, 25 FD, 200 Ohm, Biorad gene-pulser) resulting in a library size of 2.3 x 10^8 independent clones in total.

Lambda DNA-fragments from the different PCR amplifications were weighted for each ligation as follows: Each 5'-primer defines a specific group. Within these groups the 3'-primers define the subgroups. The subgroups were weighted 3:1 corresponding to the primers 3'-hu-Vlam-BlnI-SpeI-2001 : 3'-hu-Vlam2-BlnI-SpeI-2002. The groups were weighted according to their germline distribution 1:1:2:3:1:1:1:1 corresponding to the primers 5'-huVL1a-SacI-2001 : 5'-huVL1b-SacI-2001 : 5'-huVL2-SacI-2001 : 5'-huVL3/9-SacI-2001 : 5'-huVL4-SacI-2001 : 5'-huVL5-SacI-2001 : 5'-huVL6-SacI-2001 : 5'-huVL7/8-SacI-2001.

Heavy chain DNA fragments were first subcloned into pBluescript KS vector (Stratagene). To this end, eight times 400 ng of VH fragments (XhoI-BstEII digested) were each ligated with 1200 ng pBluescript KS (XhoI-BstEII digested) and transformed into electrocompetent E. coli XL1 Blue by electroporation as described for the light chains resulting in a library of 1.4 x 10^9 independent clones in total.

Heavy chain DNA-fragments from the different PCR amplifications were weighted for each ligation as follows: Each 5'-primer defines a specific group. Within these groups the 3'-primers define the subgroups. The subgroups were weighted 3:1 corresponding to the primers 3'-hu-VH-BstEII-2001 : 3'-hu-VH-J3-BstEII. The groups were weighted according to their germline distribution 7:1:1:1:0.3 corresponding to the primers 5'-huVH1,3,5-XhoI-2001 : 5'-huVH2-XhoI-2001 : 5'-huVH4-XhoI-2001 : 5'-huVH4B-XhoI-2001 : 5'-huVH6-XhoI-2001.

After electroporation each assay was incubated in SOC for phenotype expression. The different cultures were then separately incubated in 500 ml of SB selection medium containing 50 µg/ml Carbenicillin and 2 % v/v Glucose overnight. The next day, cells of each culture were harvested by centrifugation and plasmid preparation of each culture was carried out using a commercially available plasmid preparation

kit (Qiagen).

2.5. Construction of the combinatorial antibody library huLIB-ST

3600 ng of this plasmid-DNA containing the VK-library (SalI-BstEII digested; large fragment) were ligated with 1200 ng of the heavy chain V-fragments (XhoI-BstEII digested, pooled in equal amounts from restriction of the eight different pBluescript/VH-plasmid preparations) and again transformed into three 300 µl aliquots of electrocompetent *E. coli* XL1 Blue by electroporation (2.5 kV, 0.2 cm gap cuvette, 25 FD, 200 Ohm) resulting in a total VH-VK scFv (single chain variable fragment) library size of 5.4 x 10^8 independent clones.

3600 ng of this plasmid-DNA containing the Vlambda-library (SalI-BstEII digested; large fragment) were ligated with 1200 ng of the heavy chain V-fragments (XhoI-BstEII digested, pooled in equal amounts from restriction of the eight different pBluescript/VH-plasmid preparations) and again transformed into three 300 µl aliquots of electrocompetent *E. coli* XL1 Blue by electroporation (2.5 kV, 0.2 cm gap cuvette, 25 FD, 200 Ohm) resulting in a total VH-Vlambda scFv library size of 4.1 x 10^8 independent clones.

After phenotype expression and slow adaption to Carbenicillin one third of the overall kappa library and one third of the overall lambda library were each transferred into SB-Carbenicillin (50 µg/ml) selection medium; the rest was used for expansion and long term storage of the library. The Vkappa/VH-library and the Vlambda/VH-library were then infected with an infectious dose of 1 x 10^{12} particles of helper phage VCSM13 resulting in the production and secretion of filamentous M13 phage, wherein each phage particle contained single stranded pComb3H5BHis-DNA encoding a human scFv-fragment and displayed the corresponding scFv-protein as a translational fusion to phage coat protein III.

2.6. Construction of the combinatorial antibody library huLIB-STE

6 µg of this plasmid-DNA containing the VK-library (XhoI-BstEII digested; large fragment) were ligated with 2000 ng of the heavy chain V-fragments (XhoI-BstEII digested, pooled in equal amounts from restriction of the eight different pBluescript/VH-plasmid preparations) and again transformed into five 300 µl aliquots of electrocompetent *E. coli* XL1 Blue by electroporation (2.5 kV, 0.2 cm

gap cuvette, 25 FD, 200 Ohm) resulting in a total VH-VK scFv (single chain variable fragment) library size of 4.3 x 10^9 independent clones.

6 µg of the plasmid-DNA containing the Vlambda-library (XhoI-BstEII digested; large fragment) were ligated with 2 µg of the heavy chain V-fragments (XhoI-BstEII digested, pooled in equal amounts from restriction of the eight different pBluescript/VH-plasmid preparations) and again transformed into five 300 µl aliquots of electrocompetent *E. coli* XL1 Blue by electroporation (2.5 kV, 0.2 cm gap cuvette, 25 FD, 200 Ohm) resulting in a total VH-Vlambda scFv (single chain variable fragment) library size of 4.6 x 10^9 independent clones.

After phenotype expression and slow adaption to Carbenicillin one third of the overall kappa library and one third of the overall lambda library were each transferred into SB-Carbenicillin (50 µg/ml) selection medium; the rest was used for expansion and long term storage of the library. The Vkappa/VH-library and the Vlambda/VH-library were then infected with an infectious dose of 1 x 10^{12} particles of helper phage VCSM13 resulting in the production and secretion of filamentous M13 phage, wherein each phage particle contained single stranded pComb3H5BHis-DNA encoding a human scFv-fragment and displayed the corresponding scFv-protein with the N2 domain on the phage surface as a translational fusion to phage coat protein III.

2.7. Selections

Phage libraries huLIB-ST (kappa and lambda) and huLIB-STE (kappa and lambda) carrying the cloned scFv-repertoire were each harvested from the culture supernatant by PEG8000/NaCl precipitation and centrifugation.

2.7.1. Selections with huLIB-ST

For huLIB-ST approximately 1 x 10^{11} to 1 x 10^{12} kappa phages and roughly the same amount of lambda phages were each resuspended in 150 µl of TBS/1% BSA and then pooled (= phage pool 1). For phage pool 2, approximately 1 x 10^{10} to 1 x 10^{11} kappa phages and roughly the same amount of lambda phages were each resuspended in 150 µl of PBS/10% FCS and then pooled.

Selection on recombinant antigen (huLIB-ST phage pool 1)

huLIB-ST phage pool 1 was incubated with recombinant soluble human CD3

epsilon immobilized on 96 well ELISA plates. Recombinant soluble human CD3 epsilon was prepared as described in Example 1. Human CD3-epsilon normally exists in the TCR/CD3 complex as a dimer together with either the gamma or the delta subunit of the same complex. Upon dimerization with either CD3-gamma or CD3-delta, CD3-epsilon undergoes a conformational change.

The conformation of recombinant, soluble CD3-epsilon differs significantly from its native conformation in the CD3 complex (Kastrup, Scand. J. Immunol. 56 (2002), 436-42) and therefore is not significantly bound by most existing anti-CD3 antibodies (note the low ELISA signals of OKT3, SP34 and UCHT1 in binding to soluble, recombinant CD3-epsilon in Figure 14).

scFv phage that did not specifically bind to the target antigen were eliminated by up to ten washing steps with TBS/Tween. Binding entities were eluted by using HCl-Glycine pH 2.2 and after neutralization with 2 M Tris pH 12, the eluate was used for infection of a fresh uninfected *E. coli* XL1 Blue culture. Cells successfully transduced with a phagemid copy, encoding a human scFv-fragment, were again selected for Carbenicillin resistance and subsequently infected with VCMS13 helper phage to start the second round of antibody display and in vitro selection.

After five rounds of production and selection for antigen-binding scFv-displaying phage, plasmid DNA from E. coli cultures was isolated that corresponds to 3, 4 and 5 rounds of panning as well as to the unselected repertoire prior to the first round of panning.

For the production of soluble scFv-proteins two strategies were pursued:

I) ScFv-DNA fragments were excised from the plasmids (EcoRI-BsiWI), and cloned via the same restriction sites in a similar plasmid pComb3H5BFlag differing in that it adds to the expression construct (e.g. scFv) a Flag-tag (TGDYKDDDDK) instead of a His6-tag and having the phage gene III deleted.

Instead of excising the fragments from the plasmids, standard PCR amplifications of the scFv-DNA were carried out by using the previously mentioned 3'-Vkappa primers (3'-hu-Vk-J1-SpeI-BsiWI, 3'-hu-Vk-J2/4-SpeI-BsiWI, 3'-hu-Vk-J3-SpeI-BsiWI, 3'-hu-Vk-J5-SpeI-BsiWI) and the 5'-

VH-primers (5'-huVH1,3,5-XhoI-2001, 5'-huVH2-XhoI-2001, 5'-huVH4-XhoI-2001, 5'-huVH4B-XhoI-2001, 5'-huVH6-XhoI-2001). The scFv-fragments were isolated and cloned via XhoI-BsiWI- (fragments) and SalI-BsiWI-restriction (expression plasmid) into the above mentioned expression vector including the Flag-tag.

II) The isolated plasmids from the phage selection rounds were cut with BsiWI and Not I and ligated with a DNA fragment (BsiWI /Not I restricted) which added, in-frame, a murine ckappa domain, a myc tag (EEQKLISEEDL) and a His6-tag to the scFv. This ckappa/myc/His6 domain was derived by a first standard PCR using 5'-primer (5'-Mouse ckappa BsiWI (SEQ ID NO: 169)), 3'-primer (3'-Mouse-ck-myc (SEQ ID NO: 170) and murine PBMC cDNA as template. In a second standard PCR reaction the isolated product (approximately 350 bp) from the first PCR was used as template using 5'-primer (5'-Mouse ckappa BsiWI), 3'-primer (3'-myc-His6-Not (SEQ ID NO: 171). The resulting PCR-fragment was isolated (approximately 370 bp), cut with BsiWI/NotI and subcloned into a pComb3H5BHis-derivative. From this vector the ckappa/myc/His6 fragment was excised via BsiWI/NotI and used for cloning (the respective sequence is shown in Figure 1 (SEQ ID NO: 178 and SEQ ID NO: 179)).

After ligation each pool (different rounds of panning) of plasmid DNA was transformed into 100 µl heat shock competent *E. coli* XL1 Blue and plated on Carbenicillin LB- Agar. Single colonies were grown in 5 ml LB-Carb-cultures/20 mM $MgCl_2$ and expression of scFv was induced after six hours by adding Isopropyl-β-D-thiogalactosid (IPTG) to a final concentration of 1 mM and then incubated at 30 °C.

These cells were harvested after 20 hours by centrifugation and typically resuspended in 500 µl PBS. Through four rounds of freezing at –70°C and thawing at 37°C the outer membrane of the bacteria was destroyed by temperature shock so that the soluble periplasmic proteins including the scFv fusion-proteins were released into the liquid. After elimination of intact cells and cell-debris by centrifugation, the supernatant was tested by ELISA for CD3 epsilon-binding scFv-

fusion-proteins.

Detection of scFv-fragments bound to immobilized recombinant human CD3 epsilon antigen was carried out using a biotinylated anti-mouse kappa antibody (Southern Biotech, 1µg/ml PBS) detected with horseradish peroxidase-conjugated avidine (Dako, 1µg/ml PBS). The signal was developed by adding ABTS substrate solution and detected at a wavelength of 405 nm. In contrast to PBS as negative control and most of the clones after three rounds of panning, many clones after four rounds of panning already showed significant ELISA signals. Figure 2 is illustrative of typical ELISA results. In the selection of scFvs shown, construct 4-10 showed especially strong binding to recombinant CD3 epsilon antigen.

Sequence analysis showed that most of the positive clones from round 4 and 5 were closely related. Further investigations of different CD3 positive clones was therefore focused on clones of round three, since the sequence diversity of these was expected to be higher than for clones of rounds 4 and 5 (see Example 2.8).

Selection on Jurkat cells and by specific elution with recombinant antigen (huLIB-ST phage pool 2)

huLIB-ST phage pool 2 was incubated with 2 x 10^5 Jurkat cells (a CD3-positive human T-cell line) for 1 hour on ice under slow agitation. These Jurkat cells had been grown in RPMI medium enriched with fetal calf serum (10 %), glutamin and penicillin/streptomycin, harvested by centrifugation, washed in PBS and resuspended in PBS 10 % FCS. scFv phage which did not specifically bind to the Jurkat cells were eliminated by up to five washing steps with PBS/10 % FCS. Jurkat cells with bound scFv phages were then incubated with 10 µg soluble recombinant CD3 epsilon antigen for 2 hours on ice under gentle agitation. Cells were pelleted by centrifugation and the supernatant used for infection of fresh uninfected E. coli XL1 blue cells.

Cells successfully transduced with a phagemid copy encoding a human scFv-fragment were again selected for Carbenicillin resistance and subsequently infected with VCMS13 helper phage to start the second round of antibody display and in vitro selection.

After five rounds of production and selection for antigen-binding scFv-displaying

phage, plasmid DNA from E. coli cultures was isolated corresponding to 3, 4 and 5 rounds of panning as well as to the unselected repertoire prior to the first round of panning.

The cloning and expression of soluble scFvs in E. coli and the processing of the periplasmic preparations were carried out as described earlier for selection of huLIB-ST on recombinant antigen. These periplasmic preparations of single clones were then tested by ELISA for CD3epsilon-binding scFv-fusion-proteins. Detection of scFv-fragments bound to immobilized recombinant human CD3 epsilon antigen was carried out using a biotinylated anti-mouse kappa antibody (Southern Biotech, 1µg/ml PBS) detected with horseradish peroxidase-conjugated avidine (Dako, 1µg/ml PBS). The signal was developed by adding ABTS substrate solution and detected at a wavelength of 405 nm. Compared to PBS as negative control, Figure 3 shows that most of the clones after panning round 3 give significantly higher ELISA signals. Only one of the clones tested after panning round 4 and 5 showed significant binding.

2.7.2. Selections with huLIB-STE

For huLIB-STE approximately 5 x 10^{11} to 5 x 10^{12} kappa phages and roughly the same amount of lambda phage were each resuspended in 150 µl of TBS/1% BSA and then pooled (= phage pool 3). For phage pool 4, approximately 2 x 10^{11} to 2 x 10^{12} kappa phages and roughly the same amount of lambda phage were each resuspended in 150 µl of PBS/10% FCS and then pooled.

Selection on recombinant antigen (huLIB-STE phage pool 3)

huLIB-STE phage pool 3 was incubated with recombinant soluble human CD3 epsilon immobilized on 96 well ELISA plates. Recombinant soluble human CD3 epsilon was prepared as described in example 1. scFv phage which did not specifically bind to the target antigen were eliminated by up to ten washing steps with TBS/Tween. Binding entities were eluted by using HCl-Glycine pH 2.2 and after neutralization with 2 M Tris pH 12, the eluate was used for infection of a fresh uninfected *E. coli* XL1 Blue culture. Cells successfully transduced with a phagemid copy encoding a human scFv-fragment were again selected for Carbenicillin resistance and subsequently infected with VCMS13 helper phage to start the

second round of antibody display and in vitro selection. After five rounds of production and selection for antigen-binding scFv-displaying phage, plasmid DNA from E. coli cultures were isolated corresponding to 3, 4 and 5 rounds of panning as well as to the unselected repertoire prior to the first round of panning. The cloning and expression of soluble scFvs in E. coli and the processing of the periplasmic preparations were carried out as described earlier for selection of huLIB-ST on recombinant antigen.

These periplasmic preparations of single clones were then tested by ELISA for CD3epsilon-binding scFv-fusion-proteins. Detection of scFv-fragments bound to immobilized recombinant human CD3 epsilon antigen was carried out using a biotinylated anti-mouse kappa antibody (Southern Biotech, 1µg/ml PBS) detected with horseradish peroxidase-conjugated avidine (Dako, 1µg/ml PBS). The signal was developed by adding ABTS substrate solution and detected at a wavelength of 405 nm. PBS as negative control and the clones after three and four rounds of panning did not show significant ELISA signals (Figure 4). Only one clone (5-13), obtained after the fifth panning round, showed a strong signal. In further experiments positive clones could be obtained after panning round 3 and 4.

Flow cytometric analysis showed that clone 5-13 from Fig. 4 was not able to significantly bind to CD3-positive Jurkat cells. From restriction analysis of the plasmid preparations after three, four and five rounds of panning, it is probable that clones identical or at least similar to 5-13 were overgrowing other clones in rounds 4 and 5. Further investigations for different CD3-positive clones were therefore focused on clones of round three, which seems to have a higher diversity than rounds 4 and 5 (see Example 2.8).

Selection on Jurkat cells and by specific elution with recombinant antigen (huLIB-STE phage pool 4)

huLIB-STE phage pool 4 was incubated with 2 x 10^5 Jurkat cells (a CD3-positive human T-cell line) for 1 hour on ice under slow agitation. These Jurkat cells had been grown in RPMI medium enriched with fetal calf serum (10 %), glutamine and penicillin/streptomycin, harvested by centrifugation, washed in PBS and resuspended in PBS 10 % FCS. scFv phage which did not specifically bind to the

Jurkat cells were eliminated by up to five washing steps with PBS/10 % FCS. Jurkat cells with bound scFv phages were then incubated with 10 µg (100 µl) soluble recombinant CD3-epsilon antigen for 2 hours on ice under gentle agitation. Cells were pelleted by centrifugation and the supernatant was used for infection of fresh uninfected E. coli XL1 blue cells.

Cells successfully transduced with a phagemid copy encoding a human scFv-fragment were again selected for carbenicillin resistance and subsequently infected with VCMS13 helper phage to start the second round of antibody display and in vitro selection. After five rounds of production and selection for antigen-binding scFv-displaying phages, plasmid DNA from E. coli cultures was isolated corresponding to 3, 4 and 5 rounds of panning as well as to the unselected repertoire prior to the first round of panning.

The cloning and expression of soluble scFvs in E. coli and the processing of the periplasmic preparations were carried out as described earlier for selection of huLIB-ST on recombinant antigen. These periplasmic preparations of single clones were then tested by ELISA for CD3epsilon-binding scFv-fusion-proteins. Detection of scFv-fragments bound to immobilized recombinant human CD3 epsilon antigen was carried out using an anti-Flag-tag antibody (M2 Sigma 1µg/ml PBS) detected with horseradish peroxidase-conjugated polyclonal anti-mouse antibody (Dako) 1µg/ml PBS). The signal was developed by adding ABTS substrate solution and detected at a wavelength of 405 nm. Compared to the negative control, some of the clones after panning round 3 and 4 show strong ELISA signals, as seen in Figure 5. Figure 5 is illustrative of typical ELISA results. Of particular interest in Figure 5 is the identification of clone 4-48. This clone later showed positive binding to Jurkat CD3+ cells.

2.8. Screening of scFvs on CD3-positive Jurkat cells

From huLIB-ST and huLIB-STE (selections on immobilized antigen or specific elution from Jurkat cells), more than 1000 scFv-producing E. coli clones were isolated and used for periplasmic preparations as described in the next example. These scFv-containing periplasmic preparations were then screened for positive

binding signals on Jurkat cells in flow cytometric assays as described in the next example. Binding signals of positive clones were reproduced at least twice and respective scFv DNA-sequences were determined by plasmid preparation and sequencing.

The ratio of CD3-positive clones versus high sequence diversity likely reached its highest level after round 3 of panning on immobilized, solely expressed recombinant CD3 using huLIB-ST and huLIB-STE. For this reason, most of the clones that were screened originated from round 3.

From huLIB-ST and huLIB-STE pannings on Jurkat cells with selection by elution using recombinant CD3 antigen, periplasmic preparations ("PPPs") from scFv-producing E. coli clones obtained after round 3, 4 and 5 were used for screening.

Example 3: Prokaryotic expression as scFv: Binding to recombinant antigen and to human CD3-positive and negative cells

3.1. Bacterial expression in *E. coli* XL1 Blue

As previously mentioned, *E. coli* XL1 Blue transformed with pComb3H5BHis containing a VL- and VH-segment produce soluble scFv in sufficient amounts after excision of the gene III fragment and induction with 1 mM IPTG. The scFv-chain is exported into the periplasm where it folds into a functional conformation.

For periplasmic preparations the cells were grown in SB-medium supplemented with 20 mM $MgCl_2$ and carbenicillin 50 µg/ml and redissolved in PBS after harvesting. By four rounds of freezing at -70°C and thawing at 37°C, the outer membrane of the bacteria was destroyed by temperature shock and the soluble periplasmic proteins including the scFvs were released into the supernatant. After elimination of intact cells and cell-debris by centrifugation, the supernatant containing the human anti-human CD3-scFvs was collected and used for further examination. These crude supernatants containing scFv will be further termed PPP.

3.2. Binding to recombinant human CD3 epsilon antigen in ELISA

After screening experiments (see Example 2.8) the following human scFv clones

(all FLAG-tagged) were chosen for further investigation (sequences are shown in Figures 6-13, corresponding to SEQ ID NOs: 180-195):

From huLIB-ST: 4-10 (SEQ ID NO: 192, 193); 3-106 (SEQ ID NO: 180, 181); 3-114 (SEQ ID NO: 182, 183); 3-148 (SEQ ID NO: 184, 185).

From huLIB-STE: 4-48 (SEQ ID NO: 194, 195); 3-190 (SEQ ID NO: 186, 187); 3-271 (SEQ ID NO: 188, 189), 5-550 (SEQ ID NO: 190, 191).

ELISA experiments were carried out by coating the recombinant CD3 epsilon on wells of 96 well plastic plates (Nunc, maxisorb) typically at 4° C over night. The antigen was then removed, wells washed once with PBS/0.05 % Tween 20 and subsequently blocked with PBS/3 % BSA for at least one hour. After removal of the blocking solution, PPPs and control solutions were added to the wells and incubated for typically one hour at room temperature. The wells were then washed three times with PBS/0.05 % Tween 20. Detection of scFvs and control antibodies bound to immobilized antigen was carried out using a monoclonal murine anti-His6 or anti FLAG-tag antibody (Qiagen anti-PentaHis and M2 anti Flag Sigma, typically each at a final concentration of 1µg/ml PBS) detected with a peroxidase-labeled polyclonal goat anti-(mouse Fab-fragment) antibody (Dianova, 1µg/ml PBS). The signal was developed by adding ABTS substrate solution and measured at a wavelength of 405 nm. Unspecific binding of the test-samples to the blocking agent was examined by carrying out the identical assays with the identical reagents and identical timing on ELISA plates which were not coated but blocked with BSA, only. As a negative control, LK2 (a human CD3-specific svFv; described in WO 98/54440), which does not bind to the recombinant CD3 epsilon antigen, was cloned into the same phage display/expression vector pComb3H5BHis. Periplasmic preparations of L2K scFv were carried out as described for the selected scFvs.

Human CD3-specific antibodies OKT3 (Janssen Cilag GmbH), SP34 (Pharmingen) and UCHT1 (Pharmingen) were also tested for binding to the recombinant ("r") CD3-epsilon antigen (final concentrations 1 µg/ml).

Figure 14 shows the binding, measured by ELISA, of human anti-CD3 scFvs to rCD3-epsilon. It should be remembered that, prior to this ELISA experiment, these

scFv constructs have first been selected in phage display using rCD3-epsilon and then have yielded positive signals upon screening on CD3+ Jurkat cells.

As shown in Figure 14, all of the human scFvs show significantly higher binding signals than PBS, L2K-scFv (anti-CD3) control or the anti-CD3 antibodies UCHT1, SP34 and OKT3. It can be seen that the human scFvs show different intensities of ELISA signals when binding to recombinant CD3-epsilon. For example, human scFv constructs 4-10, 3-190, 4-48 and 3-550 show significantly higher ELISA signals than do human scFv constructs 3-271 and 3-106.

To exclude the possibility that the positive binding shown in Figure 14 might be due to binding to BSA (used as a blocking agent in the first ELISA experiment shown in Figure 14), a second ELISA experiment was performed in parallel. In this second ELISA experiment, all parameters were identical to those in the first ELISA experiment, except that in the second ELISA experiment no coating with antigen, but only blocking with BSA took place. The results of the second ELISA experiment are shown in Figure 15. It can clearly be seen in Figure 15 that none of the human scFvs showing binding in Figure 14 showed any significant binding to BSA.

Taken together with the positive binding on CD3+ Jurkat cells, the results shown in Figures 14 and 15 allow the conclusion that the scFvs 4-10, 3-271, 3-148, 3-190, 4-48, 3-106, 3-114, and 3-550 specifically bind to the human CD3 antigen.

3.3. Binding to CD3-positive and -negative cell lines in flow cytometric analysis

The test for binding to CD3-positive and -negative cell lines was also carried out with the periplasmic preparations:

From huLIB-ST: 4-10 (SEQ ID NO: 192, 193);
3-106 (SEQ ID NO: 180, 181);
3-114 (SEQ ID NO: 182, 183);
3-148 (SEQ ID NO: 184, 185).

From huLIB-STE: 4-48 (SEQ ID NO: 194, 195);
3-190 (SEQ ID NO: 186, 187);
3-271 (SEQ ID NO: 188, 189),
3-550 (SEQ ID NO: 190, 191).

Positive controls: L2K scFv was again included in the experiments as well as the commercially available murine anti-human CD3 antibodies OKT3, UCHT1 and SP34. PBS was used as an appropriate negative control.

The human T-cell line Jurkat and CHO cells cotransfected with both human CD3-epsilon and human CD3-gamma (CHOe/g) were used as CD3-positive cell lines. The human gastric cancer cell line KatoIII and untransfected CHO cells were included as CD3-negative cell lines.

Cell binding assays were carried out by initially incubating between 100,000 and 200,000 cells with periplasmic preparation (PPP) containing human scFv or relevant controls. After incubation the cells were washed in PBS/1 % FCS (fetal calf serum) and further incubated with 5-10 µg/ml of anti-FLAG M2 antibody. After the cells had again been washed, they were incubated with polyclonal, PE-labeled anti-mouse antibodies (Dianova) and subsequently analyzed by flow cytometry.

Figures 16-21 depict binding of human scFv constructs to various cell lines as measured by flow cytometric analysis. Each of figures 16-21 contains multiple diagrams, one for each construct tested. In any given diagram, the black distribution shows fluorescence intensity for cells incubated only with PBS alone in the absence of any construct but with all appropriate detection agents as used for detection of scFvs. In this way, any fluorescence shift observed can be definitely attributed to scFv construct rather than detection agents or buffer. Shifts in fluorescence which are indicative of construct binding to the respective cell line are depicted by a gray line in each diagram. Generally, a shift of higher magnitude away from, i.e. further to the (black) control indicates stronger binding, whereas a shift of lower magnitude away from, i.e. closer to the (black) control indicates weaker binding.

Figure 16 depicts the results of experiments measuring the binding of human scFv constructs to CD3(+) human Jurkat cells as measured by flow cytometric analysis. It can be seen that the constructs 3-148, 3-190, 3-271, 4-10 and 4-48 show clearly discernable shifts in fluorescence intensity as compared to the respective control. Constructs 3-106, 3-114 and 3-550 show only minimal, although reproducible shifts in fluorescence. The positive controls L2K scFv (anti-CD3), UCHT1, SP34 and

OKT3 all show, as expected, clearly discernable shifts in fluorescence intensity as compared to the respective control. All constructs tested therefore show binding to CD3+ cells, with 3-148, 3-190, 3-271, 4-10 and 4-48 being stronger than 3-106, 3-114 and 3-550.

Figures 17 and 18 each show the results of the test constructs' binding to CD3(-) cells. In one case (Figure 17), the CD3(-) cells are of non-human origin. In the other case (Figure 18), the CD3(-) cells are of human origin. Figure 17 depicts the results of experiments measuring the binding of human scFv constructs to CD3(-) CHO cells as measured by flow cytometric analysis. It can be seen that none of the constructs show clearly discernable shifts in fluorescence intensity as compared to the respective control, regardless of whether these constructs are scFv test constructs or the positive control constructs L2K scFv (anti-CD3), UCHT1, SP34 and OKT3. Figure 18 depicts the results of experiments measuring the binding of human scFv constructs to CD3(-) KatoIII cells as measured by flow cytometric analysis. It can be seen that none of the constructs show clearly discernable shifts in fluorescence intensity as compared to the respective control, regardless of whether these constructs are scFv constructs to be tested or the positive control constructs L2K scFv (anti-CD3 scFv), UCHT1, SP34 and OKT3.

Comparing the results from Figure 16 with those from either Figure 17 or Figure 18 indicates that the magnitudes of fluorescence shift for the constructs 3-148, 3-190, 3-271, 4-10 and 4-48 are significantly less when binding to CD3(-) cells than when binding to CD3(+) cells. Taken together with the ELISA results described above, it can therefore be concluded that at least the human scFv constructs 3-148, 3-190, 3-271, 4-10 and 4-48 bind to the native human CD3 on human CD3+ cells.

To further confirm the specificity of the scFv constructs, binding studies were also performed using CHO cells which had been cotransfected with both CD3-epsilon ("CD3-e") and CD3-gamma ("CD3-g"). Non-transfected CHO cells express neither CD3-e nor CD3-g. CHO cells transfected with both CD3-e and CD3-g express these two proteins much more weakly than do Jurkat cells. For this reason, using CHO cells tranfected with CD3-e and CD3-g confers a higher degree of stringency on the binding experiments than would be possible using Jurkat cells.

Figures 19-21 depict the results of such binding studies as measured by flow cytometric analysis. Figure 19 depicts the results of binding by the scFv construct 3-271 to CD3(+) Jurkat cells. Figure 20 depicts the results of binding by the scFv construct 3-271 to CHO cells lacking CD3 antigen. Figure 21 depicts the results of binding by the scFv construct 3-271 to CHO cells transfected with both CD3-epsilon and CD3-gamma. Therefore, the only difference between non-transfected CHO cells and CHO cells doubly transfected with CD3-epsilon and CD3-gamma is the presence of CD3-e and CD3-g on the doubly transfected cells. Considering Figures 19 and 21, it is clear that interaction of scFv construct 3-271 with Jurkat cells (Figure 19) and with CHO cells doubly transfected with CD3-epsilon and CD3-gamma (Figure 21) in each case gives rise to a strong fluorescence shift away from the control. In contrast, the interaction of scFv 3-271 with non-transfected CHO cells (Figure 20) gives rise to no significant fluorescence shift as compared to those observed in Figures 19 and 21. This emphasizes the specificity for CD3 previously shown for the scFv construct 3-271.

It should not be forgotten that the human scFv construct 3-271 showed a weak signal in the ELISA experiment using recombinant CD3-epsilon as antigen (Figure 14). Taken together with the strong binding manifested by 3-271 on CD3(+) Jurkat cells, it becomes clear that CD3 epsilon likely makes up only part of the epitope recognized by 3-271. Without being bound by theory, it is therefore believed that the epitope specifically recognized by human scFv construct 3-271 comprises CD3-epsilon as well as at least another subunit of the CD3 complex.

Similar experiments were performed for the remaining human scFv constructs, but these constructs were unable to significantly bind to CHO cells transfected with CD3-epsilon and CD3-gamma. This finding is most likely due to the lower activity of these constructs as compared to the construct 3-271 as well as to the fact that the level of expression of CD3 on the transfected CHO cells is much lower than that on Jurkat CD3+ cells. This assumption is supported by the weaker binding, in Figure 21, of positive controls UCHT1, OKT3, SP34 and scFv L2K (anti-CD3) to the transfected CHO cells.

Example 4: Eukaryotic expression of human anti-human CD3 binding specificity as part of bispecific single chain constructs: Testing the biological activity as T-cell engagers against various target cells

In order to test whether the human anti-CD3 molecules as disclosed herein above retain their biological activity in a more complicated molecular context, various bispecific single chain antibody molecules comprising anti-CD3 specificity were prepared. Each bispecific single chain antibody comprised a human scFv specifically binding to the human CD3 antigen as well as another molecular domain which specifically binds to an antigen other than the human CD3 antigen. Expression in bacteria might lead to functionally less active bispecific single chain antibodies.

Mammalian cells were used for the production of functional bispecific antibodies. To this end, the chosen human anti-human CD3 scFvs were cloned into the eukaryotic expression vector pEFDHFR (Mack, Proc. Natl. Acad. Sci. U.S.A. 92 (1995) 7021-5) already containing a target specificity, for example anti-CD19 (e.g. VH-VL as in Figure 23), anti-EpCAM (e.g. 5-10 from WO 99/25818, e.g. VH-VL as in Figure 22), anti-CD20 (e.g. as in Figure 24) or anti-CCR5 (e.g. as in Figure 25).

4.1. Cloning of bispecific single chain constructs against human CD3 and human CD19

In order to create a model to test the chosen human anti-human CD3 scFvs as part of a bispecific antibody, nucleic acid sequences encoding these human anti-human CD3 scFvs were cloned into a eukaryotic expression vector in translational fusion to an scFv antibody fragment directed against human CD19.

4.1.1. Construction of antiCD3-antiCD19 bispecific single chain antibodies

The pEFDHFR vector containing the DNA sequence coding for mouse anti-human CD3 x anti-human CD19 was used to generate corresponding human anti-CD3 constructs wherein the human anti-CD3 portion was expressed co-linearly with and N-terminal to the anti-CD19 portion in the resulting bispecific single chain antibody construct (biscFv).

To replace the mouse anti-human CD3 specificity in VH-VL configuration with the selected human anti-human CD3 specificity, the appropriate restriction sites had to

be introduced into the human anti-human CD3-constructs by PCR. The primers 5'-5BVH-BsrGI (SEQ ID NO: 172) and 3'-5BVL-BspEI (SEQ ID NO: 173) added a BsrGI-site to the 5-prime VH-domain and a BspEI-site to the 3' VL-domain, respectively.

The PCR amplified DNA-fragments were then purified. These fragments and the vector anti-human CD19 pEFDHFR were restricted with BrsGI and BspEI (NEB enzymes) and ligated after purification in an appropriate ratio. The ligation was transformed into E. coli XLI blue by heatshock transformation and clones were screened with the vector-specific primer leader seq and the insert-specific primer 3'-5BVL-BspEI. Positive clones were inoculated in 50 ml of SB-medium containing carbenicillin as a selection marker and were grown overnight at 37°C in a shaker. Plasmid preparation was carried out using a commercial kit (QIAGEN plasmid midi kit) before the constructs were finally checked by sequencing.

In this way, the following biscFv-constructs were prepared:

- Human anti-CD3 3-148 VH-VL x anti-CD19 VL-VH (nucleic acid: Table 1, Construct 20nuc; amino acid: Table 2, Construct 20prot; SEQ ID NOS: 205, 206)
- Human anti-CD3 3-190 VH-VL x anti-CD19 VL-VH (nucleic acid: Table 1, Construct 28nuc; amino acid: Table 2, Construct 28prot; SEQ ID NOS: 207, 208)
- Human anti-CD3 3-271 VH-VL x anti-CD19 VL-VH (nucleic acid: Table 1, Construct 36nuc; amino acid: Table 2, Construct 36prot; SEQ ID NOS: 209, 210)
- Human anti-CD3 4-10 VH-VL x anti-CD19 VL-VH (nucleic acid: Table 1, Construct 52nuc; amino acid: Table 2, Construct 52prot; SEQ ID NOS: 211, 212)
- Human anti-CD3 4-48 VH-VL x anti-CD19 VL-VH (nucleic acid: Table 1, Construct 60nuc; amino acid: Table 2, Construct 60prot; SEQ ID NOS: 213, 214)

4.1.2. Construction of antiCD19-antiCD3 bispecific single chain antibodies

The pEFDHFR vector containing the DNA sequence coding for anti-human CD19 x

mouse – anti-human CD3 was used as a vector backbone for subcloning.

To replace the VHVL mouse anti-human CD3-epsilon specificities with the selected human anti-human CD3-specificities the appropriate restriction sites had to be introduced into the human anti-human CD3-constructs by PCR and cloning into intermediate vectors. First, to introduce an XhoI-site to clones derived from selection within the library huLIB-ST, PCR was carried out on the anti-human CD3-pComb3H5BFlag-constructs using the specific 5'-VH and 3'-VK-J-primers corresponding to their individual sequence. The amplified DNA-fragments were cloned by restriction with XhoI and BsiWI enzymes (both from Roche) into pComb3H5BFlag. Anti-human CD3-pComb3H5BFlag constructs were then digested with BspEI (NEB) and BsiWI and the approximately 750 – 800 bp scFv DNA-fragments were isolated. The scFv fragment 4-10 was then ligated into an intermediate cloning vector 3B10 pEFDHFRHis which had been restricted with the same enzymes. This step introduced a His-Tag followed by a SalI restriction site, the latter being necessary for the next cloning step.

Both 3B10 (anti-EpCAM) x anti-human CD3 4-10 pEFDHFR-His and the anti-CD19-bearing vector mentioned above were restricted with SalI (Roche) and BspEI(NEB). The scFv DNA fragment 4-10 His and the vector fragment of anti-CD19 pEFDHFR were isolated and then ligated in an appropriate ratio. The ligation was transformed into E. coli XLI blue by heatshock transformation, and clones were screened with the vector-specific primer leader seq and the insert-specific primer 3'-5BVL-BspEI. Positive clones were inoculated in 50 ml of SB-medium containing carbenicillin as a selection marker and grown overnight at 37°C in a shaker.

Plasmid preparation was carried out using a commercial kit (QIAGEN plasmid midi kit) before the constructs were finally checked by sequencing. The isolated BspEI-BsiWI fragments of the other human CD3-specific clones (3-148, 3-190, 3-271, 4-48) were then cloned into the anti-CD19 x anti-CD3 4-10 pEFDHFR via the same cloning sites in place of 4-10. Finally, the following biscFv-constructs were generated:

- anti-CD19 VL-VH x human anti-CD3 3-148 VH-VL (nucleic acid: Table 1,

Construct 21nuc; amino acid: Table 2, Construct 21prot; SEQ ID NOS: 215, 216)

- anti-CD19 VL-VH x human anti-CD3 3-190 VH-VL (nucleic acid: Table 1, Construct 29nuc; amino acid: Table 2, Construct 29prot; SEQ ID NOS: 217, 218)
- anti-CD19 VL-VH x human anti-CD3 3-271 VH-VL (nucleic acid: Table 1, Construct 37nuc; amino acid: Table 2, Construct 37prot; SEQ ID NOS: 219, 220)
- anti-CD19 VL-VH x human anti-CD3 4-10 VH-VL (nucleic acid: Table 1, Construct 53nuc; amino acid: Table 2, Construct 53prot; SEQ ID NOS: 221, 222)
- anti-CD19 VL-VH x human anti-CD3 4-48 VH-VL (nucleic acid: Table 1, Construct 61nuc; amino acid: Table 2, Construct 61prot; SEQ ID NOS: 223, 224)

4.2. Cloning of bispecific sc-constructs against huCD3 and huEpCAM

4.2.1. Construction of antiCD3-antiEpCAM bispecific single chain antibodies

The pEFDHFR vector containing the sequence coding for mouse anti-human CD3 x 5-10 (anti human-EpCAM) was used as a vector backbone for subcloning.

To replace the mouse anti-human CD3-epitope in VH/VL configuration with the selected human anti-human CD3 specificities, the appropriate restriction sites had to be introduced into the human anti-human CD3-constructs by standard PCR and DNA from the human CD3-binders as template. The primers 5'-5BVH-BsrGI (SEQ ID NO: 172) and 3'-5BVL-BspEI (SEQ ID NO: 173) added a BsrGI-site to the 5' VH-domain and a BspEI-site to the 3'-VL-domain, respectively.

The PCR-amplified DNA fragments were then purified. These fragments and the pEFDHFR vector containing the DNA-fragment coding for mouse anti-CD3 x 5-10 were restricted with BrsGI and BspEI (NEB enzymes) and were ligated after purification in an appropriate ratio. The ligation was transformed into E. coli XLI blue by heatshock transformation and clones were screened with the vector-specific primer leader sequence and the insert-specific primer 3'-5BVL-BspEI (SEQ ID NO: 173).

Positive clones were inoculated into 50 ml of SB-medium containing carbenicillin as a selection-marker and grown overnight at 37°C in a shaker. Plasmid preparation was carried out using a commercial kit (QIAGEN plasmid midi kit) before the constructs were finally checked by sequencing. In this way, the following biscFv-constructs were generated:

- Human anti-CD3 3-148 VH-VL x anti-EpCAM 5-10 VH-VL (nucleic acid: Table 3, Construct 82nuc; amino acid: Table 4, Construct 82prot; SEQ ID NOS: 225, 226)
- Human anti-CD3 3-190 VH-VL x anti- EpCAM 5-10 VH-VL (nucleic acid: Table 3, Construct 90nuc; amino acid: Table 4, Construct 90prot; SEQ ID NOS: 227, 228)
- Human anti-CD3 3-271 VH-VL x anti- EpCAM 5-10 VH-VL (nucleic acid: Table 3, Construct 98nuc; amino acid: Table 4, Construct 98prot; SEQ ID NOS: 229, 230)
- Human anti-CD3 4-10 VH-VL x anti- EpCAM 5-10 VH-VL (nucleic acid: Table 3, Construct 114nuc; amino acid: Table 4, Construct 114prot; SEQ ID NO: 231, 232)
- Human anti-CD3 4-48 VH-VL x anti- EpCAM 5-10 VH-VL (nucleic acid: Table 3, Construct 122nuc; amino acid: Table 4, Construct 122prot; SEQ ID NOS: 233, 234)

4.2.2. Construction of anti-EpCAM x anti-CD3 bispecific single chain antibodies

The pEFDHFR vector containing the sequence coding for mouse anti-human CD3 x 5-10 (anti human-EpCAM) was used as a vector backbone for subcloning.

To create the desired constructs, an intermediate cloning was necessary to insert the required restriction site SalI. First, the 5' mouse anti-human CD3 scFv-domain was exchanged with another 5-10 domain to create a suitable intermediate cloning vector 5-10 x 5-10 pEFDHFR.

For the insert, the vector 5-10 x mouse (anti-human CD3) pEFDHFR was restricted with the restriction enzymes BsrGI and BspEI. The excised and purified fragment was then ligated into the vector mentioned above, which had been restricted with

the same enzymes. The resulting construct 5-10 x 5-10 pEFDHFR could than be used for further cloning of human anti-human CD3-epitopes at the C-terminus of 5-10 by restricting the latter with BspEI and SalI.

The chosen human anti-human CD3-specificities were taken from the pEFDHFR constructs containing the sequence mouse anti-human CD19 x human anti-human CD3 which were created as described in Example 4.1.2 . The 3' anti-CD3-domains were restricted from the vector with BspEI and SalI and were ligated into 5'- 5-10 pEFDHFR (x BspEI-SalI) in an appropriate ratio.

The ligation was transformed into E. coli XLI blue by heatshock transformation, clones were screened with the vector-specific primers leader seq and EF pol. Positive clones were inoculated in 50 ml of SB-medium containing carbenicillin as a selection marker and grown overnight at 37°C in a shaker. Plasmid preparation was carried out using a commercial kit (QIAGEN plasmid midi kit) before the constructs were finally checked by sequencing.

In this way, the following biscFv-constructs were generated:

- anti-EpCAM 5-10 VL-VH x human anti-CD3 3-148 VH-VL (nucleic acid: Table 3, Construct 85nuc; amino acid: Table 4, Construct 85prot; SEQ ID NOS: 235, 236)
- anti- EpCAM 5-10 VL-VH x human anti-CD3 3-190 VH-VL (nucleic acid: Table 3, Construct 93nuc; amino acid: Table 4, Construct 93prot; SEQ ID NOS: 237, 238)
- anti- EpCAM 5-10 VL-VH x human anti-CD3 3-271 VH-VL (nucleic acid: Table 3, Construct 101nuc; amino acid: Table 4, Construct 101prot; SEQ ID NOS: 239, 240)
- anti- EpCAM 5-10 VL-VH x human anti-CD3 4-10 VH-VL (nucleic acid: Table 3, Construct 117nuc; amino acid: Table 4, Construct 117prot; SEQ ID NOS: 241, 242)
- anti- EpCAM 5-10 VL-VH x human anti-CD3 4-48 VH-VL (nucleic acid: Table 3, Construct 125nuc; amino acid: Table 4, Construct 125prot; SEQ ID NOS: 243, 244)

Primers used for cloning of anti-target/anti-CD3 bispecific antibodies were 5'-

5BVH-BsrGI (SEQ ID NO: 172) and 3'-5BVL-BspEI (SEQ ID NO: 173). The leader seq is shown in SEQ ID NO: 204.

4.3. Cloning of bispecific single chain constructs against human CD3 and human CD20

Human CD3-specificities were combined with a single chain directed against the human CD20 antigen in an analogous manner as described herein above for the cloning of anti-CD19 (or anti-EpCAM) x human anti-human CD3 and human anti-human CD3 x anti-CD19 (or anti-EpCAM). The following examples of such constructs were generated:

- anti-CD20 VL-VH x human anti-CD3 3-190 VH-VL (nucleic acid: Table 7, Construct 221nuc; amino acid: Table 8, Construct 221prot; SEQ ID NOs: 245, 246)
- anti-CD20 VL-VH x human anti-CD3 3-148 VH-VL (nucleic acid: Table 7, Construct 213nuc; amino acid: Table 8, Construct 213prot; SEQ ID NOs: 247, 248)

4.4. Cloning of bispecific single chain constructs against human CD3 and human CCR5

Human CD3-specificities were combined with a single chain directed against the human CCR5 antigen in an analogous manner as described herein above for the cloning of anti-CD19 (or anti-EpCAM) x human anti-human CD3 and human anti-human CD3 x anti-CD19 (or anti-EpCAM). The following examples are generated:

- anti-CCR5 VL-VH x human anti-CD3 3-190 VH-VL (nucleic acid: Table 5, Construct 157nuc; amino acid: Table 7, Construct 157prot; SEQ ID NOs: 249, 250)
- anti-CCR5 VL-VH x human anti-CD3 3-148 VH-VL (nucleic acid: Table 5, Construct 149nuc; amino acid: Table 7, Construct 149prot; SEQ ID NOs: 251, 252)

4.5. Expression and purification of the respective bispecific single chain constructs in CHO cells

Before transfection, DHFR-negative CHO cells were grown in alpha MEM-medium

((Bio Whittaker) +10 % FCS +glutamine + Penicillin/Streptomycin) containing a mix of nucleosides. The day before transfection, $4x10^5$ cells/3 ml were seeded in a sterile 6-well cell culture plastic plate and grown overnight in supplemented medium.

Transient transfection was carried out using the PolyFect® Transfection Reagent (QIAGEN) following the manufacturer's instructions. The cells were incubated for four days, followed by harvesting of the supernatants. After sedimentation of cells by centrifugation and transfer into fresh tubes, the supernatants could be tested for binding in an ELISA- and/or FACS-assay.

For stable transfection after collecting the transiently produced supernatants, CHO cells were transferred into a small cell-culture bottle (25 cm^2) and grown in selection medium (alpha-MEM without nucleosides). Cells were expanded (75 cm^2 culture flask) in this medium and finally grown in a 150 cm^2 cell culture flask to confluence. Cells from one 150 cm^2 culture flask were then transferred to plastic roller bottles with 500 ml HyQ®-medium (HyClone; serumfree, containing Penicilin/Streptomycin) and grown for 7 days before harvest of the cell culture supernatant. The cells were removed by centrifugation and the supernatant containing the expressed protein was stored at –20°C.

4.6. Purification of the bispecific single chain constructs

The single chain bispecific antibodies were isolated in a two step purification process of immobilized metal affinity chromatography (IMAC) and gel filtration. All constructs were purified according to this method. Äkta® FPLC System (Pharmacia) and Unicorn® Software were used for chromatography. All chemicals were of research grade and purchased from Sigma (Deisenhofen) or Merck (Darmstadt).

IMAC was performed using a Fractogel® column (Merck) which was loaded with $ZnCl_2$ according to the protocol provided by the manufacturer. The column was equilibrated with buffer A2 (20 mM sodium phosphate pH 7.5, 0.4 M NaCl) and the cell culture supernatant (500 ml) was applied to the column (10 ml) at a flow rate of 3 ml/min. The column was washed with buffer A2 to remove unbound sample. Bound protein was eluted using a 2 step gradient of buffer B2 (20 mM sodium

phosphate pH 7.5, 0.4 M NaCl, 0.5 M Imidazol) according to the following:
Step 1: 20% buffer B2 in 6 column volumes;
Step 2: 100% buffer B2 in 6 column volumes.
Eluted protein fractions from step 2 were pooled for further purification.
Gel filtration chromatography was performed on a Sephadex S200 HiPrep column (Pharmacia) equilibrated with PBS (Gibco). Eluted protein samples (flow rate 1 ml/min) were subjected to standard SDS-PAGE and Western Blot for detection. Prior to purification, the column was calibrated for molecular weight determination (molecular weight marker kit, Sigma MW GF-200). Protein concentrations were determined using protein assay dye (MicroBCA, Pierce) and IgG (Biorad) as standard protein.
Purified bispecific protein was analyzed by SDS PAGE under reducing conditions performed with pre-cast 4-12% Bis Tris gels (Invitrogen). Sample preparation and application were performed according to the protocol provided by the manufacturer. The molecular weight was determined with MultiMark protein standard (Invitrogen). The gel was stained with colloidal Coomassie (Invitrogen protocol). Western Blot was performed using an Optitran® BA-S83 membrane and the Invitrogen Blot Module according to the protocol provided by the manufacturer. The antibodies used were directed against the His Tag (Penta His, Qiagen) and goat-anti-mouse Ig labeled with alkaline phosphatase (AP) (Sigma), and BCIP/NBT (Sigma) as substrate. The single chain bispecific antibody could be specifically detected by Western Blot.

4.7. Bioactivity of bispecific antibodies specific for CD19 and CD3

Cytotoxic activity of the bispecific antibodies was determined in a fluorochrome release based cytotoxicity assay. For this experiment purified biscFv 3-190 x anti-CD19 P2 (protein fraction 2 from gel filtration) was used.

CD19 positive NALM6 cells were used as target cells ($1.5x10^7$) labeled with 10 µM calcein AM (Molecular Probes, Leiden, Netherland, no. C-1430) for 30 min at 37°C in cell culture medium. After two washes in cell culture medium, cells were counted and mixed with cells from the CD4-positive T cell clone CB15 (kindly provided by

Dr. Fickenscher, University of Erlangen/Nuernberg, Germany). 2 x 10^6 CB15 cells and 2 x 10^5 Nalm6 cells were mixed per ml (E:T ratio of 1:10) and 50 µl of this suspension were used per well in a 96 well round bottom plate. biscFv 3-190 x anti-CD19 P2 was diluted in RPMI/10% FCS in a dilution series and 50 µl of the respective solution were added to the cell suspension. The same dilution series was performed using PBS as negative control, starting with the same volume as for biscFv 3-190 x anti-CD19 P2. A standard reaction was incubated at 37°C/5% CO2 for 2 hours. After the cytotoxic reaction, the released dye in the incubation medium was quantitated in a fluorescence reader (Tecan, Crailsheim, Germany) and compared with the fluorescence signal from a control reaction (without bispecific antibody), and the fluorescence signal obtained for totally lysed cells (for 10 min in 1% saponin). On the basis of these readings, the specific cytotoxicity was calculated according to the following formula: [Fluorescence (Sample) - Fluorescence (Control)] : [Fluorescence (Total Lysis)- Fluorescence (Control)] x 100.

Sigmoidal dose response curves typically had R2 values >0.97 as determined by Prism Software (GraphPad Software Inc., San Diego, USA; EC50 values calculated by the analysis program were used for comparison of bioactivity).

As shown in Figure 26 the anti-human CD3 x anti-CD19 biscFv mediated cytotoxic activity against the CD19-positive NALM6-cells using CB15 cells as effector cells. In this experiment half maximal toxicity could be obtained in the low ng/ml concentrations of the biscFv 3-190 x anti-CD19. Control dilutions with PBS instead of biscFv did not show significant cytotoxicity. Based on the results shown in Figure 26, it can therefore be concluded that the anti-human CD3 x anti-CD19 biscFv binds to the CD19 antigen on target cells and to the CD3 antigen on the effector inducing lysis of target.

4.8. Bioactivity of bispecific antibodies specific for EpCAM and CD3

For this experiment anti-CD3 3-271 x 5-10 anti-EpCAM P2 (protein fraction 2 from gel filtration), anti-CD3 3-271 x 5-10 anti-EpCAM P3 (protein fraction 3 from gelfiltration), 5-10 anti-EpCAM x anti-CD3 3-148 (main protein fraction from gelfiltration) and 5-10 anti-EpCAM x anti-CD3 3-190 P3 (protein fraction 3 from

gelfiltration) were evaluated with respect to their ability to mediate specific toxicity. Anti-CD3 3-190 x anti-CD19 P2 (protein fraction 2 from gelfiltration) which proved to mediate specific cytotoxicity to CD19-positive NALM6-cells (see Figure 26) was included as an appropriate negative control for CD19-negative CHO-EpCAM cells. M79, an anti-EpCAM x anti-CD3 biscFv construct (Mack, PNAS 92 (1995), 7021-5), was used as a positive control.

CHO cells from the American Type Cell Culture Collection (ATCC, Manassas, USA) were transfected with epithelial cell adhesion molecule (EpCAM). A cell clone derived from this transfection, referred to as CHO-EpCAM cells, was used for the experiments. Untransfected CHO cells were also included in this experiment to demonstrate the EpCAM specificity of the cytotoxicity to the EpCAM-transfected cells. The CD4-positive T cell clone CB15 was kindly provided by Dr. Fickenscher, University of Erlangen/Nuernberg, Germany. Cells were cultured as recommended by the suppliers.

4.9. Flow cytometry-based cytotoxicity assay

Untransfected CHO as well as CHO-EpCAM ($1.5x10^7$) cells were respectively washed free of serum two times with PBS and incubated with PKH26 dye (Sigma-Aldrich Co.) according to the manufacturer's instructions. After staining, cells were washed two times with RPMI/10% FCS. Cells were counted and mixed with CB15 effector cells. The resulting cell suspension contained 400,000 target and 2×10^6 effector cells per ml. 50 µl of the mixture was used per well in a 96 well round bottom plate. Antibody constructs were diluted in RPMI/10% FCS to the required concentration and 50 µl of this solution were added to the cell suspension. A standard reaction was incubated for 16 h at 37°C / 5% CO_2. Propidium iodide was added to a final concentration of 1 µg/ml. After 10 min of incubation at room temperature, cells were analyzed by flow cytometry. PKH26 fluorescence was used for positive identification of target cells. Cytotoxicity was measured as ratio of PI positive over all target cells.

Specific cytotoxicity mediated by the purified biscFv-constructs was plotted in Figure 27. This figure shows the mediation of a significant specific cytotoxicity by the anti-human CD3 x anti-human EpCAM biscFvs as well as by the positive

control M79 x CD3 (Mack Proc Natl Acad Sci USA 92 (1995), 7021-5) on EpCAM-transfected CHO-cells. No relevant specific lysis could be obtained on non-transfected CHO cells as well as in case of the CHO-EpCAM cells irrelevant biscFv 3-190 x anti CD19.

In the cytotoxicity experiments shown in Figure 26 and 27 it is clearly demonstrated that the respective human anti-CD3 binders, combined with a target specificity in the context of a bispecific single chain construct, are able to mediate specific toxicity to target cells by recruiting CD3-positive effector cells. This not only corroborates the CD3 specificity of the respective human anti-CD3 constructs themselves, but also clearly demonstrates the retention of this specificity as well as T cell triggering potential within a bispecific single chain antibody format.

Claims

1. A method for the preparation of a human binding molecule, fragment or derivative thereof which specifically binds to the human CD3 complex, said method comprising the steps of:
   (a) selecting molecules specifically binding to/interacting with the extracellular domain of the recombinant ε-chain, expressed independent of the human CD3 complex in the absence of other members of said CD3 complex, from a population of candidate polypeptides encoded by a library;
   (b) selecting molecules from a population identified in step (a) for binding to the human CD3 complex; and
   (c) preparation of said selected binding molecule.

2. The method of claim 1, further comprising the step (d) identifying the nucleic acid sequence encoding said binding molecule in the library.

3. The method of claim 1 or 2, wherein the library which encodes the candidate polypeptides is derived from a DNA-library or an RNA-library.

4. The method of any of claims 1 to 3, wherein the library which encodes the candidate polypeptides is derived from primary of secondary lymphatic organs of humans.

5. The method of any of claims 1 to 4, wherein the selection of the human binding molecules is effected by exposing the human binding molecules to immobilized recombinant, solely expressed ε- chain, expressed independent of the human CD3 complex in the absence of other members of said CD3 complex.

6. The method of any of claims 1 to 5, wherein said selection comprises a phage display method.

7. The method of any of claims 1 to 6, wherein said human binding molecule, fragment or derivative thereof is an antibody molecule, antibody fragment or derivative thereof or a construct comprising at least one antibody, antibody fragment or derivative thereof which specifically binds to the human CD3 complex.

8. The method of claim 7, wherein said derivative of an antibody is an scFv.

9. The method of claim 7 or 8, wherein said antibody molecule, antibody fragment, derivative thereof or construct comprises at least one further antigen-interaction-site and/or at least one further effector domain.

10. The method of claim 9, wherein said antibody molecule, antibody fragment, derivative thereof or construct is humanized and/or deimmunized in an additional step.

11. The method of claims 9 or 10, wherein said further antigen-interaction-site is specific for one or more cell surface molecule.

12. The method of claim 11, wherein said cell surface molecule is a tumor specific marker.

13. The method of claims 9 to 12, wherein said at least one further antigen-interaction-site is a further scFv.

14. The method of claims 9 to 13, wherein said at least one further antigen-interaction-site specifically binds to/interacts with an antigen selected from the group consisting of EpCAM, CCR5, CD19, EphA2, HER-2 neu, HER-3, HER-4, EGFR, PSMA, CEA, , MUC-1 (mucin), MUC2, MUC3, MUC4,

$MUC5_{AC}$, $MUC5_B$, MUC7, βhCG, Lewis-Y, CD20, CD33, CD30, ganglioside GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, Carboanhydrase IX (MN/CA IX), CD44v6, Sonic Hedgehog (Shh), Wue-1, Plasma Cell Antigen, (membrane-bound) IgE, Melanoma Chondroitin Sulfate Proteoglycan (MCSP), CCR8, TNF-alpha precursor, STEAP, mesothelin, A33 Antigen, Prostate Stem Cell Antigen (PSCA), Ly-6; desmoglein 4, E-cadherin neoepitope, Fetal Acetylcholine Receptor, CD25, CA19-9 marker, CA-125 marker and Muellerian Inhibitory Substance (MIS) Receptor type II, sTn (sialylated Tn antigen; TAG-72), FAP (fibroblast activation antigen), endosialin, EGFRvIII, LG, SAS and CD63.

15. The method of any of claims 2 to 14, further comprising the step of recombinant expression of the binding molecule, fragment or derivative thereof encoded by a nucleic acid sequence selected from the group consisting of:

(a) the identified nucleic acid sequence;

(b) a nucleic acid sequence hybridizing with the complementary strand of the nucleic identified nucleic acid sequence under stringent hybridization conditions;

(c) a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (a) and (b).

16. The method of claim 15, wherein said step of recombinant expression of the binding molecule, fragment or derivative thereof encoded by a nucleic acid sequence comprises the preparation of a vector comprising said nucleic acid sequence.

17. The method of claim 16, wherein said vector further comprises a nucleic acid sequence which is a regulatory sequence operably linked to said identified nucleic acid sequence.

18. The method of claim 16 or 17, wherein the vector is an expression vector.

19. The method of any of claims 16 to 18, further comprising the step of transforming a host with said vector.

20. The method of any of claims 15 to 19, further comprising the step of isolation and/or purification of the recombinantly expressed human binding molecule, fragment or derivative thereof.

21. The method of any of claims 1 to 20, further comprising the step of formulating the human binding molecule as a pharmaceutical composition, which optionally further comprises a pharmaceutically acceptable carrier or diluent.

22. A human binding molecule specifically binding to/interacting with the human CD3 complex, whereby said binding molecule is an antibody molecule, antibody fragment or derivative thereof or an antibody construct.

23. The human binding molecule of claim 22, wherein said derivative of an antibody is an scFv.

24. The human binding molecule according to claim 22 or 23, wherein said antibody molecule, antibody fragment or derivative thereof or an antibody construct, comprises a variable V_H-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 1,17, 33, 49, 65, 81, 97 and 113 or a variable V_H-region having an amino acid sequence as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98 and 114.

25. The human binding molecule according to claim 22 or 23, wherein said antibody molecule, antibody fragment or derivative thereof or an antibody construct, comprises a variable V_L-region as encoded by a nucleic acid molecule as shown in a SEQ ID NO selected from the group consisting of

SEQ ID NOs: 9, 25, 41, 57, 73, 89, 105 and 121 or a variable V_L-region having an amino acid sequence as shown in a SEQ ID NO selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106 and 122.

26. The human binding molecule according to any of claims 22 to 25, wherein said antibody molecule, antibody fragment or derivative thereof or an antibody construct, comprises at least one CDR3 of an V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 7, 23, 39, 55, 71, 87, 103 or 119 or at least one CDR3 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104 or 120 and/or wherein said antibody molecule comprises at least one CDR3 of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 15, 31, 47, 63, 79, 95, 111 or 127 or at least one CDR3 amino acid sequence of an V_L-region as shown in SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112 or 128.

27. The human binding molecule according to any of claims 22 to 25, wherein said antibody molecule, antibody fragment or derivative thereof or an antibody construct, comprises at least one CDR2 of an V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 5, 21, 37, 53, 69, 85, 101 or 117 or at least one CDR2 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102 or 118 and/or wherein said antibody molecule comprises at least one CDR2 of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 13, 29, 45, 61, 77, 93, 109 or 125 or at least one CDR2 amino acid sequence of an V_L-region as shown in SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110 or 126.

28. The human binding molecule according to any of claims 22 to 25, wherein said antibody molecule, antibody fragment or derivative thereof or an antibody construct, comprises at least one CDR1 of an V_H-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 3, 19, 35, 51, 67, 83, 99 or 115 or at least one CDR1 amino acid sequence of an V_H-region as shown in SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100 or 116 and/or

wherein said antibody molecule comprises at least one CDR1 of an V_L-region as encoded by a nucleic acid molecule as shown in SEQ ID NOs: 11, 27, 43, 59, 75, 91, 107 or 123 or at least one CDR1 amino acid sequence of an V_L-region as shown in SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108 or 124.

29. The human binding molecule according to any of claims 22 to 28, additionally comprising at least one further antigen-interaction-site and/or at least one further effector domain.

30. The human binding molecule according to claim 29, which is humanized and/or deimmunized.

31. The human binding molecule according to claim 29 or 30, wherein said at least one further antigen-interaction-site is specific for one or more cell surface molecule.

32. The human binding molecule according to claim 31, wherein said cell surface molecule is a tumor specific marker.

33. The human binding molecule according to any of claims 29 to 32, wherein said at least one further antigen-interaction-site is a further scFv.

34. The human binding molecule according to any of claims 29 to 33, wherein said at least one further antigen-interaction-site specifically binds to/interacts with an antigen selected from the group consisting of EpCAM, CCR5, CD19, EphA2, HER-2 neu, HER-3, HER-4, EGFR, PSMA, CEA, , MUC-1 (mucin), MUC2, MUC3, MUC4, $MUC5_{AC}$, $MUC5_B$, MUC7, βhCG, Lewis-Y, CD20, CD33, CD30, ganglioside GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, Carboanhydrase IX (MN/CA IX), CD44v6, Sonic Hedgehog (Shh), Wue-1, Plasma Cell Antigen, (membrane-bound) IgE, Melanoma Chondroitin Sulfate Proteoglycan (MCSP), CCR8, TNF-alpha precursor, STEAP, mesothelin, A33 Antigen, Prostate Stem Cell Antigen

(PSCA), Ly-6; desmoglein 4, E-cadherin neoepitope, Fetal Acetylcholine Receptor, CD25, CA19-9 marker, CA-125 marker and Muellerian Inhibitory Substance (MIS) Receptor type II, sTn (sialylated Tn antigen; TAG-72), FAP (fibroblast activation antigen), endosialin, EGFRvIII, LG, SAS and CD63.

35. The human binding molecule according to claim 34, wherein said further antigen binding site specifically binds to/interacts with the CD19 molecule.

36. The human binding molecule according to claim 35, comprising an amino acid sequence selected from the group of

(a) an amino acid sequence corresponding to construct 1prot to 64prot of table 2;

(b) (b) an amino acid sequence encoded by a nucleic acid sequence corresponding to construct 1nuc to 64nuc of table 1;

(c) an amino acid sequence encoded by a nucleic acid sequence hybridizing with the complementary strand of a nucleic acid sequence as defined in (b) under stringent hybridization conditions; and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c).

37. The human binding molecule according to claim 34, wherein said further antigen binding site specifically binds to/interacts with the EpCAM molecule.

38. The human binding molecule according to claim 37, comprising an amino acid sequence selected from the group of

(a) an amino acid sequence corresponding to construct 65prot to 128prot of table 4;

(b) an amino acid sequence encoded by a nucleic acid sequence corresponding to construct 65nuc to 128nuc of in table 3;

(c) an amino acid sequence encoded by a nucleic acid sequence hybridizing with the complementary strand of a nucleic acid sequence as defined in

(b) under stringent hybridization conditions;and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c).

39. The human binding molecule according to claim 34, wherein said further antigen binding site specifically binds to/interacts with the CCR5 molecule.

40. The human binding molecule according to claim 39, comprising an amino acid sequence selected from the group of

(a) an amino acid sequence corresponding to construct 129prot to 192prot of table 6;

(b) an amino acid sequence encoded by a nucleic acid sequence corresponding to construct 129nuc to 192nuc of table 5;

(c) an amino acid sequence encoded by a nucleic acid sequence hybridizing with the complementary strand of a nucleic acid sequence as defined in (b) under stringent hybridization conditions; and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c).

41. The human binding molecule according to claim 34, wherein said further antigen binding site specifically binds to/interacts with the CD20 molecule.

42. The human binding molecule according to claim 41, comprising an amino acid sequence selected from the group of

(a) an amino acid sequence corresponding to construct 193prot to 256prot of table 8;

(b) an amino acid sequence encoded by a nucleic acid sequence corresponding to construct 193nuc to 256nuc of table 7;

(c) an amino acid sequence encoded by a nucleic acid sequence hybridizing with the complementary strand of a nucleic acid sequence as

defined in (b) under stringent hybridization conditions; and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (b) and (c).

43. The human binding molecule according to any of claim 22 to 42, wherein said binding molecule is obtainable by a method according to any of claims 1 to 21.

44. A nucleic acid sequence encoding a human binding molecule according to any of claims 22 to 42.

45. The nucleic acid molecule of claim 44 comprising a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence encoding the mature form of a protein comprising the amino acid sequence of human binding molecule of the invention, preferably as given in SEQ ID Nos: 181, 183, 185, 187, 189, 191, 193, 195, 206, 208, 210, 212, 214, 216, 218, 220, 222, 224, 226, 228, 230, 232, 234, 236, 238, 240, 242, 244, 246, 248, 250 or 252;

(b) a nucleotide sequence comprising or consisting of the DNA sequence as given in SEQ ID NOs: 180, 182, 184, 186, 188, 190, 192, 194, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249 or 251;

(c) a nucleotide sequence hybridizing with the complementary strand of a nucleotide sequence as defined in (b) under stringent hybridization conditions;

(d) a nucleotide sequence encoding a protein derived from the protein encoded by a nucleotide sequence of (a) or (b) by way of substitution, deletion and/or addition of one or several amino acids of the amino acid sequence encoded by the nucleotide sequence of (a) or (b);

(e) a nucleotide sequence encoding a protein having an amino acid

sequence at least 60 % identical to the amino acid sequence encoded by the nucleotide sequence of (a) or (b);

(f) a nucleotide sequence which is degenerate as a result of the genetic code to a nucleotide sequence of any one of (a) to (e);

46. A vector comprising a nucleic acid sequence according to claim 44 or 45.

47. The vector of claim 46, which further comprises a nucleic acid sequence which is a regulatory sequence operably linked to said nucleic acid sequence according to claim 44 or 45.

48. The vector of claim 46 or 47, wherein the vector is an expression vector.

49. A host transformed or transfected with a vector according to any of claims 46 to 48.

50. A process for the production of a human binding molecule according to any of claims 22 to 42 said process comprising culturing a host of claim 49 under conditions allowing the expression of the polypeptide construct and recovering the produced polypeptide construct from the culture.

51. A composition comprising a human binding molecule according to any of claims 22 to 42 or as produced by the process of claim 50, a nucleic acid molecule of claim 44 or 45, a vector of any one of claims 46 to 48 or a host of claim 49 and, optionally, a proteinaceous compound capable of providing an activation signal for immune effector cells.

52. The composition of claim 51 which is a pharmaceutical composition further comprising, optionally, suitable formulations of carrier, stabilizers and/or excipients.

53. The composition of claim 51 which is a diagnostic composition further comprising, optionally, means and methods for detection.

54. Use of a human binding molecule according to any of claims 22 to 42 or as produced by the process of claim 50, a nucleic acid molecule of claim 44 or 45, a vector of any one of claims 46 to 48 or a host of claim 49 for the preparation of a pharmaceutical composition for the prevention, treatment or amelioration of a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, viral disease, allergic reactions, parasitic reactions, graft-versus-host diseases or host-versus-graft diseases.

55. A method for the prevention, treatment or amelioration a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, viral disease, allergic reactions, parasitic reactions, graft-versus-host diseases or host-versus-graft diseases in a subject in the need thereof, said method comprising the step of administration of an effective amount a human binding molecule according to any of claims 22 to 42 or as produced by the process of claim 50, a nucleic acid molecule of claim 44 or 45, a vector of any one of claims 46 to 48 or a host of claim 49.

56. The method of claim 55, wherein said subject is a human.

57. The method of claim 55 or 56 further comprising, the administration of a proteinaceous compound capable of providing an activation signal for immune effector cells.

58. The method of claim 57, wherein said proteinaceous compound is administered simultaneously or non-simultaneously with a human binding molecule according to any of claims 22 to 42 or as produced by the process

of claim 50, a nucleic acid molecule of claim 44 or 45, a vector of any one of claims 46 to 48 or a host of claim 49.

59. A kit comprising a human binding molecule according to any of claims 22 to 42 or as produced by the process of claim 50, a nucleic acid molecule of claim 44 or 45, a vector of any one of claims 46 to 48 or a host of claim 49.

```
BsiWI
~~~~~~~
     R  T  D  A  A  P  T     V  S  I     F  P  P  S  S  E  Q     L  T  S
1    CGTACGGATG CTGCACCAAC TGTATCCATC TTCCCACCAT CCAGTGAGCA GTTAACATCT
     GCATGCCTAC GACGTGGTTG ACATAGGTAG AAGGGTGGTA GGTCACTCGT CAATTGTAGA

     G  G  A  S  V  V  C     F  L  N     N  F  Y  P  K  D  I     N  V  K
61   GGAGGTGCCT CAGTCGTGTG CTTCTTGAAC AACTTCTACC CCAAAGACAT CAATGTCAAG
     CCTCCACGGA GTCAGCACAC GAAGAACTTG TTGAAGATGG GGTTTCTGTA GTTACAGTTC

     W  K  I  D  G  S  E     R  Q  N     G  V  L  N  S  W  T     D  Q  D
121  TGGAAGATTG ATGGCAGTGA ACGACAAAAT GGCGTCCTGA ACAGTTGGAC TGATCAGGAC
     ACCTTCTAAC TACCGTCACT TGCTGTTTTA CCGCAGGACT TGTCAACCTG ACTAGTCCTG

     S  K  D  S  T  Y  S     M  S  S     T  L  T  L  T  K  D     E  Y  E
181  AGCAAAGACA GCACCTACAG CATGAGCAGC ACCCTCACGT TGACCAAGGA CGAGTATGAA
     TCGTTTCTGT CGTGGATGTC GTACTCGTCG TGGGAGTGCA ACTGGTTCCT GCTCATACTT
```

Fig. 1

```
                R  H  N  S  Y  T  C  E  A  T  H  K  T  S  T  S  P  I  V  K
241   CGACATAACA GCTATACCTG TGAGGCCACT CACAAGACAT CAACTTCACC CATTGTCAAG
      GCTGTATTGT CGATATGGAC ACTCCGGTGA GTGTTCTGTA GTTGAAGTGG GTAACAGTTC

                S  F  N  R  N  E  C  E  E  Q  K  L  I  S  E  E  D  L  H  H
301   AGCTTCAACA GGAATGAGTG TGAGGAACAG AAGCTGATCT CAGAGGAAGA TCTGCATCAC
      TCGAAGTTGT CCTTACTCAC ACTCCTTGTC TTCGACTAGA GTCTCCTTCT AGACGTAGTG

                        NotI
                H  H  H  H  * ~~~~~~~~~~
361   CACCATCACC ATTAAGCGGC CGC
      GTGGTAGTGG TAATTCGCCG GCG
```

Fig. 1 (cont.)

Fig. 2

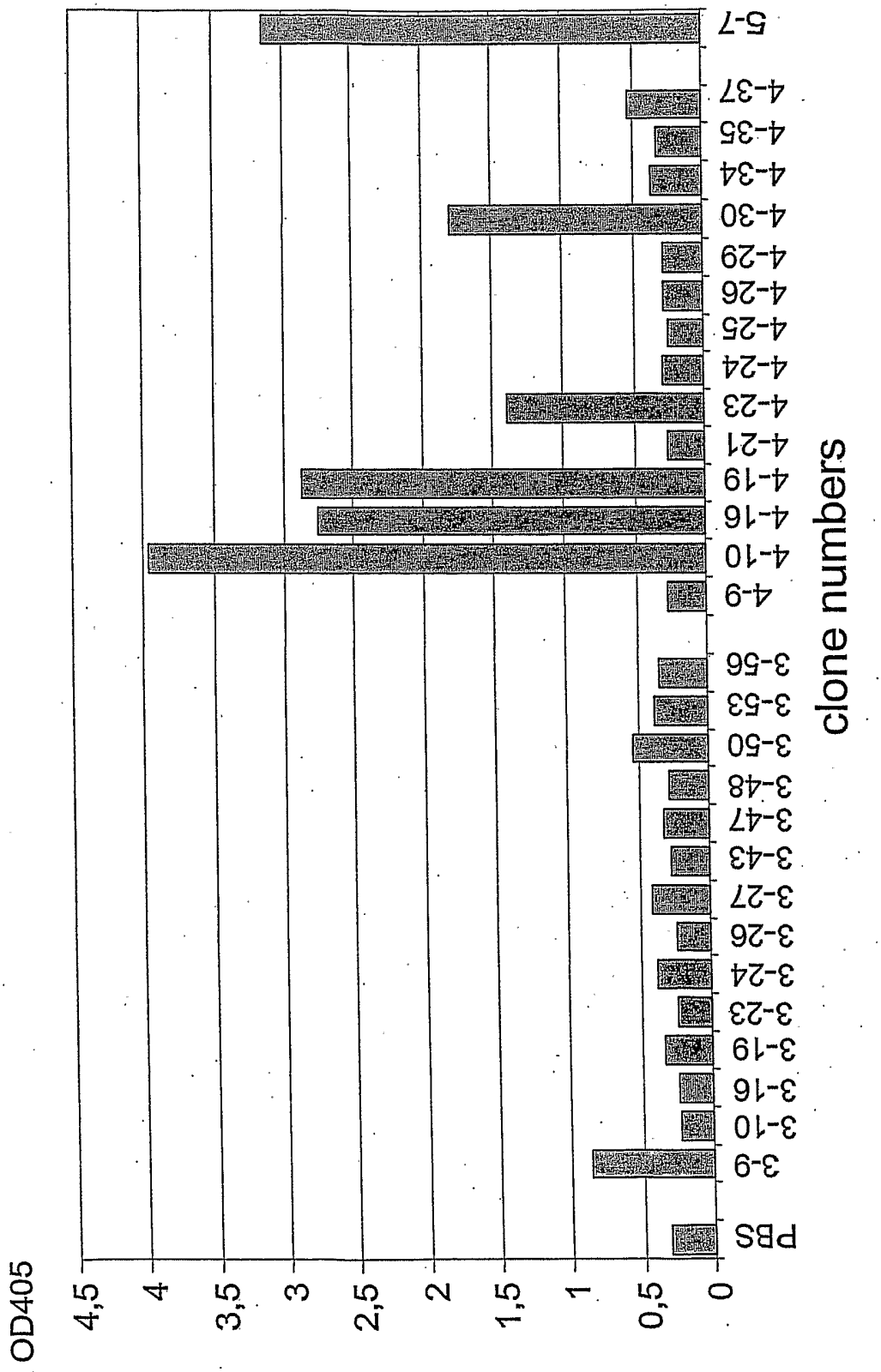

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clone numbers

Fig. 3

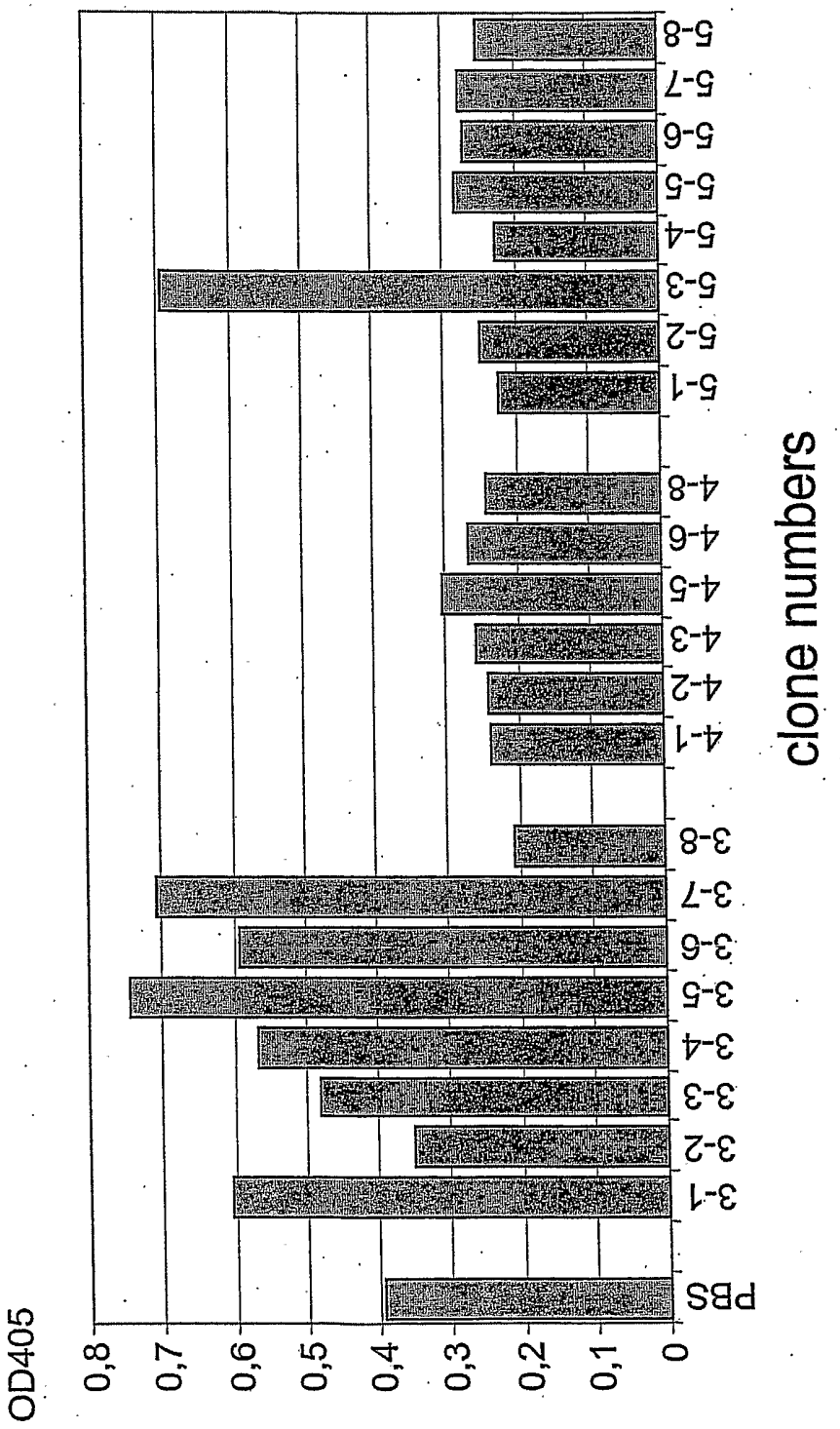

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clone numbers

Fig. 4

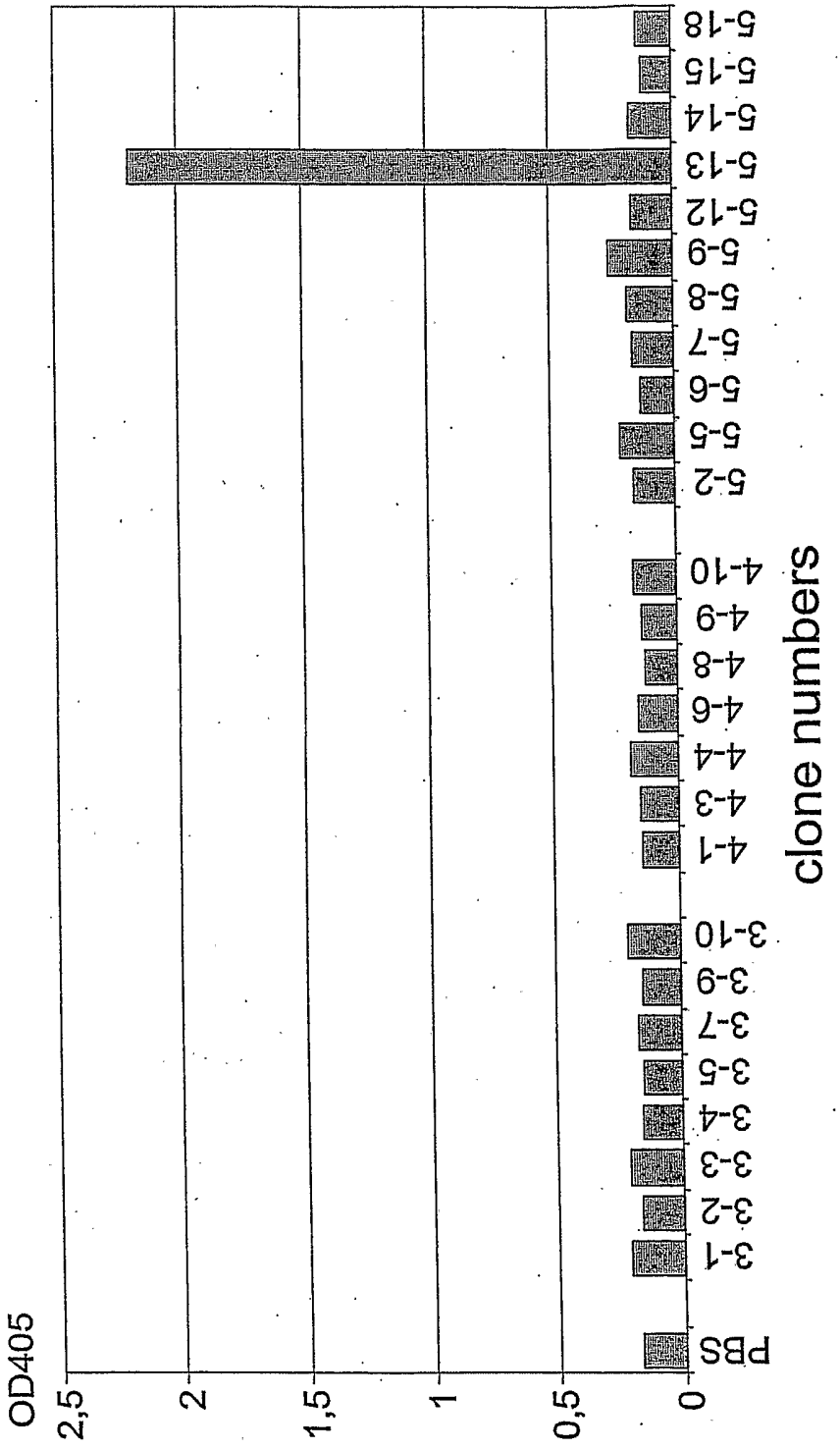
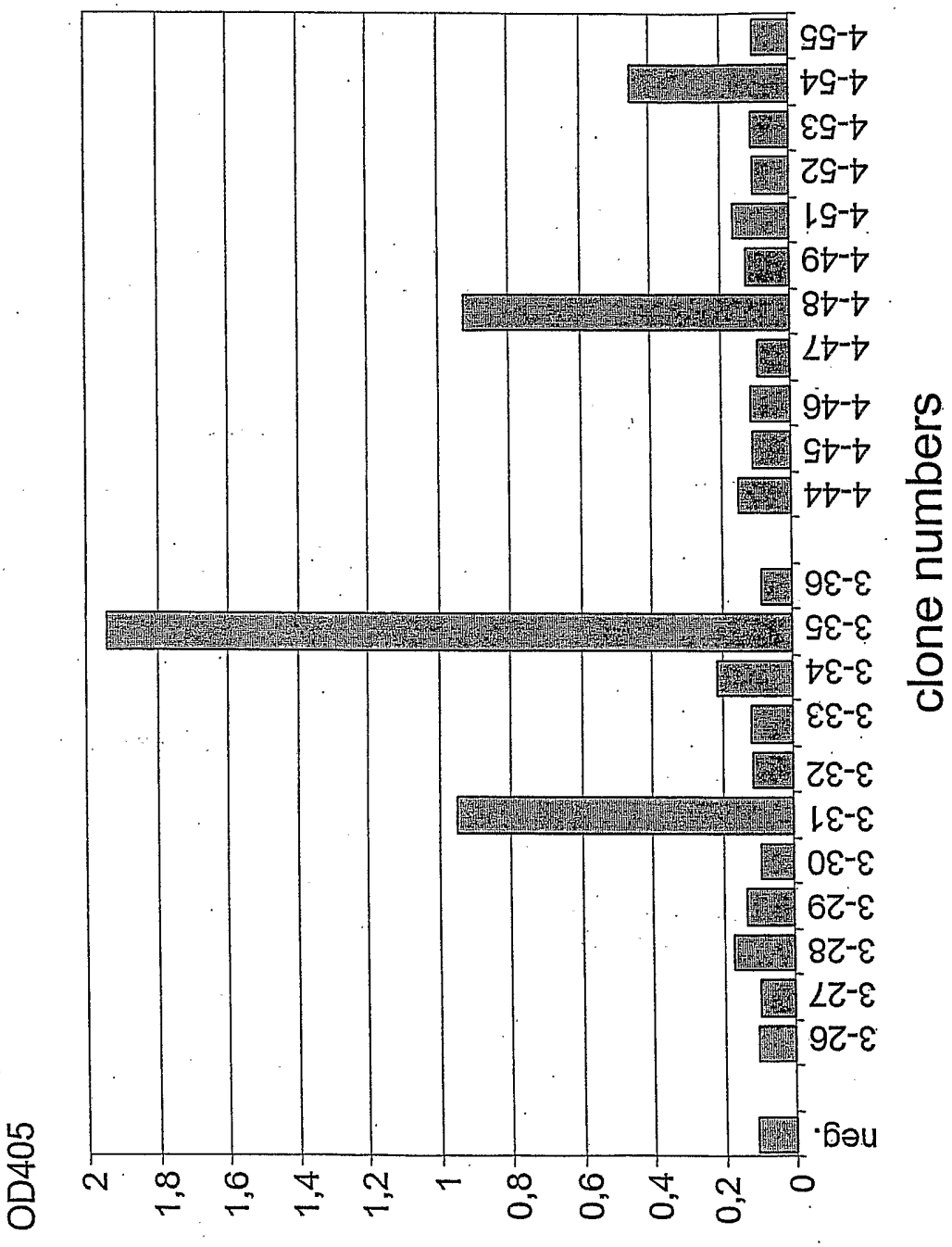

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clone numbers

Fig. 5


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clone numbers

3-106

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                E  L  Q  L  V  E  S     G  G  G     V  V  Q  P     G  R  S     L  R  L
    1   GAGCTGCAGC TGGTCGAGTC TGGGGGAGGC GTGGTCCAGC CTGGGAGGTC CCTGAGACTC
        CTCGACGTCG ACCAGCTCAG ACCCCCTCCG CACCAGGTCG GACCCTCCAG GGACTCTGAG

                                                  VH-CDR1
                S  C  A  A     S  G  F     T  F  S     S  Y  G  M  H     W  V     R  Q  A
   61   TCCTGTGCAG CCTCTGGATT CACCTTCAGT AGCTATGGCA TGCACTGGGT CCGCCAGGCT
        AGGACACGTC GGAGACCTAA GTGGAAGTCA TCGATACCGT ACGTGACCCA GGCGGTCCGA

                                                                        VH-CDR2
                P  G  K  G     L  E  W     V  A     V     I  S  Y  D     G  S  N     K  Y  Y
  121   CCAGGCAAGG GGCTGGAGTG GGTGGCAGTT ATATCATATG ATGGAAGTAA TAAATACTAC
        GGTCCGTTCC CCGACCTCAC CCACCGTCAA TATAGTATAC TACCTTCATT ATTTATGATG

                A  D  S  V     K  G     R     F  T  I     S  R  D  N     S  K  N     T  L  Y
  181   GCAGACTCCG TGAAGGGCCG ATTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT
        CGTCTGAGGC ACTTCCCGGC TAAGTGGTAG AGGTCTCTGT TAAGGTTCTT GTGCGACATA
```

Fig. 6

```
                L  Q  M  N  S  L  R  S. E  D  T  A  V  Y  Y  C  A  R  L  S
241             CTGCAAATGA ACAGCCTGAG ATCTGAGGAC ACGGCCGTGT ATTACTGTGC GAGGCTCAGC
                GACGTTTACT TGTCGGACTC TAGACTCCTG TGCCGGCACA TAATGACACG CTCCGAGTCG

VH-CDR3
                P  Y  C  T  N  G  V  C  W  D  A  F  D  I  W  G  Q  G  T  M
301             CCGTATTGTA CTAATGGTGT ATGCTGGGAT GCTTTTGATA TCTGGGGCCA AGGGACAATG
                GGCATAACAT GATTACCACA TACGACCCTA CGAAAACTAT AGACCCCGGT TCCCTGTTAC

                V  T  V  S  S  G  G  G  G  G  S  G  G  G  G  S  G  G  G  S
361             GTCACCGTCT CCTCAGGTGG TGGTGGTTCT GGCGGCGGCG GCTCCGGTGG TGGTGGTTCT
                CAGTGGCAGA GGAGTCCACC ACCACCAAGA CCGCCGCCGC CGAGGCCACC ACCACCAAGA

                E  L  Q  M  T  Q  S  P  S  S  L  S  A  S  V  G  D  R  V  S
421             GAGCTCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTCGGAGA CAGAGTCTCC
                CTCGAGGTCT ACTGGGTCAG AGGTAGGAGG GACAGACGTA GACAGCCTCT GTCTCAGAGG
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Fig. 6 (cont.)

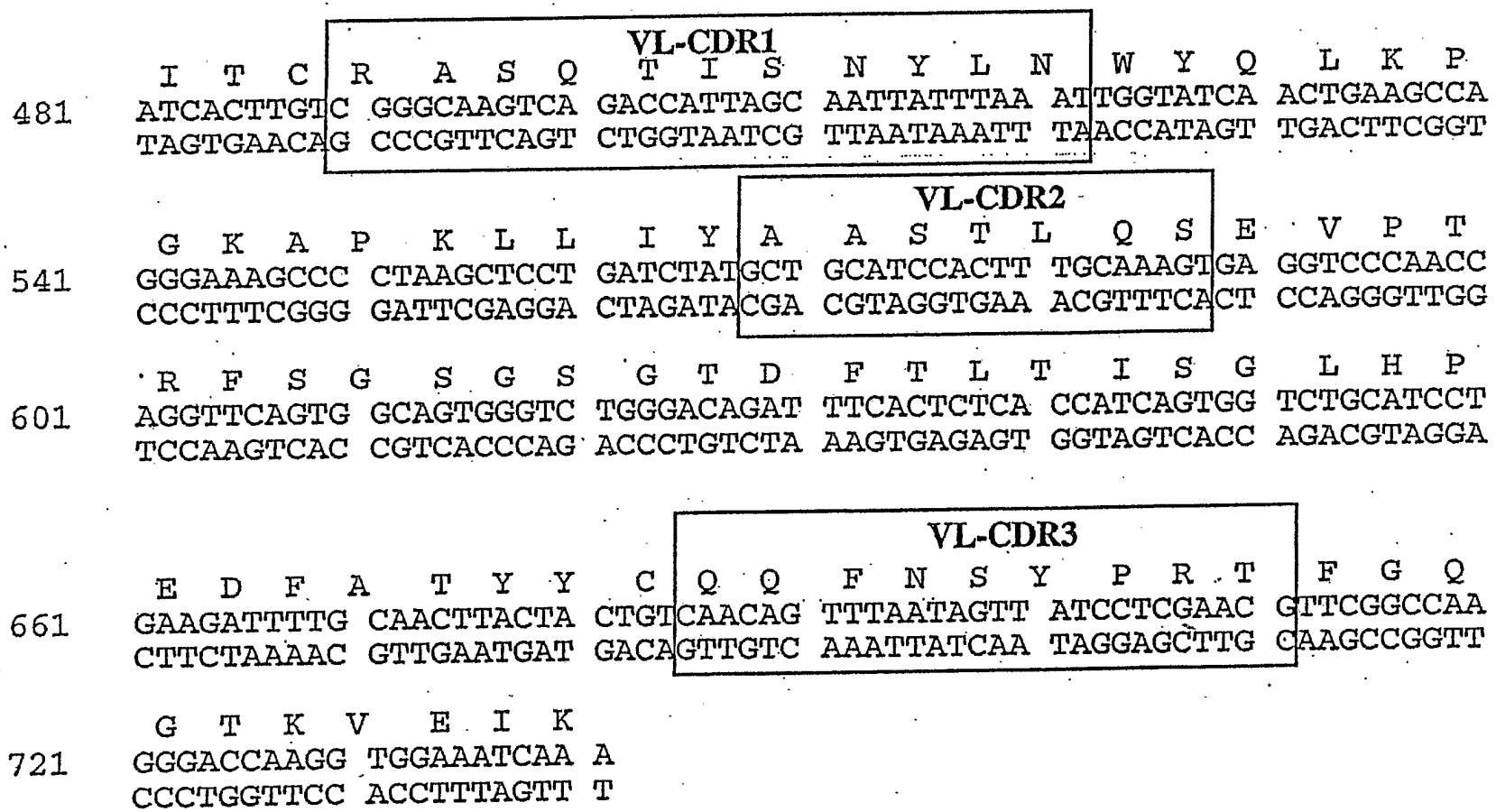

VL-CDR1
VL-CDR2
VL-CDR3
I T C R A S Q T I S N Y L N W Y Q L K P
481 ATCACTTGTC GGGCAAGTCA GACCATTAGC AATTATTTAA ATTGGTATCA ACTGAAGCCA
TAGTGAACAG CCCGTTCAGT CTGGTAATCG TTAATAAATT TAACCATAGT TGACTTCGGT
G K A P K L L I Y A A S T L Q S E V P T
541 GGGAAAGCCC CTAAGCTCCT GATCTATGCT GCATCCACTT TGCAAAGTGA GGTCCCAACC
CCCTTTCGGG GATTCGAGGA CTAGATACGA CGTAGGTGAA ACGTTTCACT CCAGGGTTGG
R F S G S G S G T D F T L T I S G L H P
601 AGGTTCAGTG GCAGTGGGTC TGGGACAGAT TTCACTCTCA CCATCAGTGG TCTGCATCCT
TCCAAGTCAC CGTCACCCAG ACCCTGTCTA AAGTGAGAGT GGTAGTCACC AGACGTAGGA
E D F A T Y Y C Q Q F N S Y P R T F G Q
661 GAAGATTTTG CAACTTACTA CTGTCAACAG TTTAATAGTT ATCCTCGAAC GTTCGGCCAA
CTTCTAAAAC GTTGAATGAT GACAGTTGTC AAATTATCAA TAGGAGCTTG CAAGCCGGTT
G T K V E I K
721 GGGACCAAGG TGGAAATCAA A
CCCTGGTTCC ACCTTTAGTT T

Fig. 6 (cont.)

3-114

```
          E  L  Q  L     V  E  S     G  G  G     L  V  K  P     G  R  S     L  R  L
1     GAGCTGCAGC TGGTCGAGTC TGGGGGAGGC TTGGTAAAGC CAGGGCGGTC CCTGAGACTC
      CTCGACGTCG ACCAGCTCAG ACCCCCTCCG AACCATTTCG GTCCCGCCAG GGACTCTGAG

                                                  VH-CDR1
          S  C  T  A     S  G  F     T  F  G     D  Y  A  M     S  W  F     R  Q  A
61    TCCTGTACAG CTTCTGGATT CACCTTTGGT GATTATGCTA TGAGCTGGTT CCGCCAGGCT
      AGGACATGTC GAAGACCTAA GTGGAAACCA CTAATACGAT ACTCGACCAA GGCGGTCCGA

                                                                        VH-CDR2
          P  G  K  G     L  E  W     V  G     F     I  R  S  K     A  Y  G     G  T  T
121   CCAGGGAAGG GGCTGGAGTG GGTAGGTTTC ATTAGAAGCA AAGCTTATGG TGGGACAACA
      GGTCCCTTCC CCGACCTCAC CCATCCAAAG TAATCTTCGT TTCGAATACC ACCCTGTTGT

          E  Y  A  A     S  V  K     G  R  F     I  S  R  D     D  S  K     S  I
181   GAATACGCCG CGTCTGTGAA AGGCAGATTC ACCATCTCAA GAGATGATTC CAAAAGCATC
      CTTATGCGGC GCAGACACTT TCCGTCTAAG TGGTAGAGTT CTCTACTAAG GTTTTCGTAG
```

Fig. 7

```
                A  Y  L  Q  M  N  S  L  K  T  E  D  T  A  V  Y  Y  C  T  P
241   GCCTATCTGC AAATGAACAG CCTGAAAACC GAGGACACAG CCGTGTATTA CTGTACTCCA
      CGGATAGACG TTTACTTGTC GGACTTTTGG CTCCTGTGTC GGCACATAAT GACATGAGGT

                          VH-CDR3
                Q  L  W  L  L  Q  D  A  F  D  I  W  G  Q  G  T  M  V  T  V
301   CAGCTATGGT TACTACAAGA TGCTTTTGAT ATCTGGGGCC AAGGGACAAT GGTCACCGTC
      GTCGATACCA ATGATGTTCT ACGAAAACTA TAGACCCCGG TTCCCTGTTA CCAGTGGCAG

                S  S  G  G  G  G  S  G  G  G  G  S  G  G  G  G  S  E  L  Q
361   TCCTCAGGTG GTGGTGGTTC TGGCGGCGGC GGCTCCGGTG GTGGTGGTTC TGAGCTCCAG
      AGGAGTCCAC CACCACCAAG ACCGCCGCCG CCGAGGCCAC CACCACCAAG ACTCGAGGTC

                M  T  Q  S  P  S  S  L  S  A  S  V  G  D  R  V  T  I  T  C
421   ATGACCCAGT CTCCATCCTC CCTGTCTGCA TCTGTAGGAG ATAGAGTCAC CATCACTTGC
      TACTGGGTCA GAGGTAGGAG GGACAGACGT AGACATCCTC TATCTCAGTG GTAGTGAACG

                          VL-CDR1
                R  A  S  Q  G  I  S  N  Y  L  A  W  Y  Q  Q  K  P  G  K  V
481   CGGGCGAGTC AGGGCATTAG CAATTATTTA GCCTGGTATC AGCAGAAACC AGGGAAAGTT
      GCCCGCTCAG TCCCGTAATC GTTAATAAAT CGGACCATAG TCGTCTTTGG TCCCTTTCAA
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Fig. 7 (cont.)

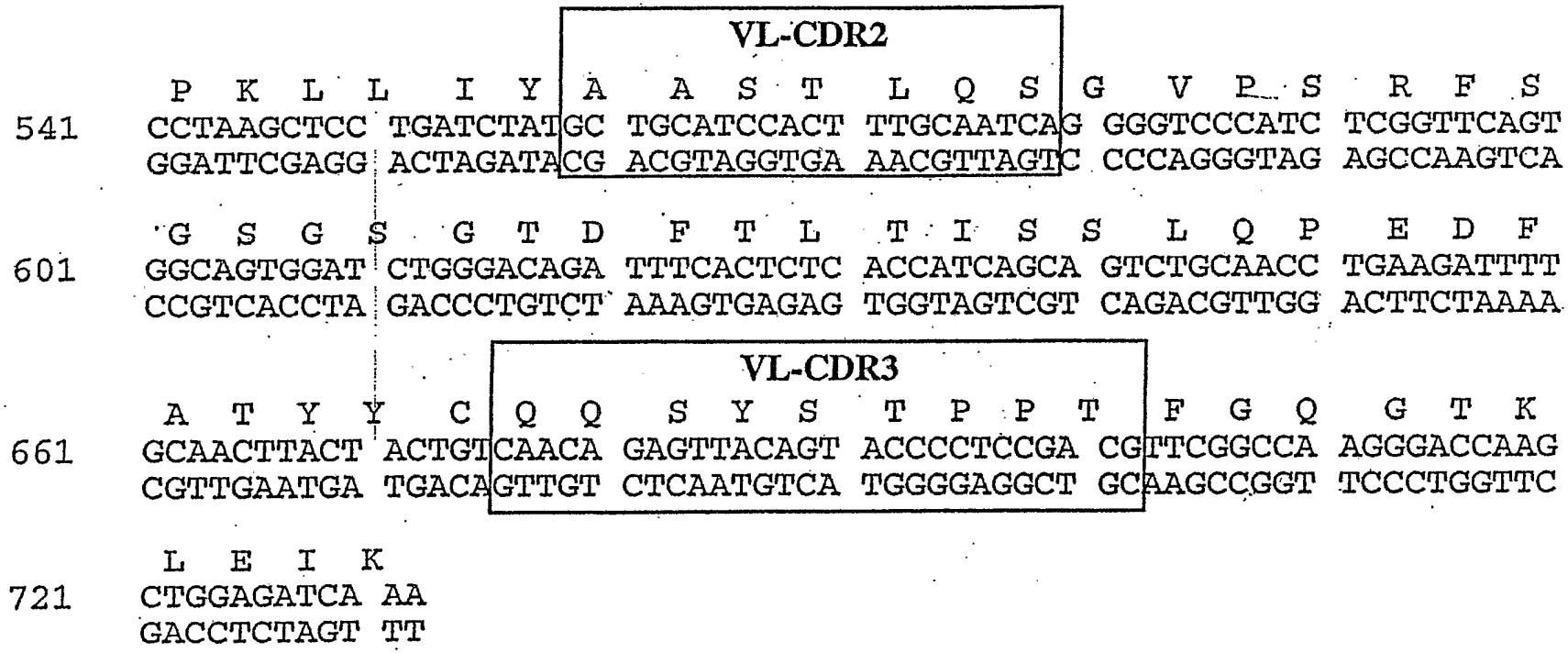

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GGATTCGAGG ACTAGATACG ACGTAGGTGA AACGTTAGTC CCCAGGGTAG AGCCAAGTCA
G S G S G T D F T L T I S S L Q P E D F
601 GGCAGTGGAT CTGGGACAGA TTTCACTCTC ACCATCAGCA GTCTGCAACC TGAAGATTTT
CCGTCACCTA GACCCTGTCT AAAGTGAGAG TGGTAGTCGT CAGACGTTGG ACTTCTAAAA
VL-CDR3
A T Y Y C Q Q S Y S T P P T F G Q G T K
661 GCAACTTACT ACTGTCAACA GAGTTACAGT ACCCCTCCGA CGTTCGGCCA AGGGACCAAG
CGTTGAATGA TGACAGTTGT CTCAATGTCA TGGGGAGGCT GCAAGCCGGT TCCCTGGTTC
L E I K
721 CTGGAGATCA AA
GACCTCTAGT TT

Fig. 7 (cont.)

3-148

```
          E  L  Q  L  V  E  S     G  P  G     L  V  K  P     S  G  T     L  S  L
1   GAGCTGCAGC TGGTCGAGTC TGGCCCAGGA CTGGTGAAGC CTTCGGGGAC CCTGTCCCTC
    CTCGACGTCG ACCAGCTCAG ACCGGGTCCT GACCACTTCG GAAGCCCCTG GGACAGGGAG

                                                VH-CDR1
          T  C  A  V     S  G  G     S  I  S     S  R  N  W     W  S  W     V  R  Q
61  ACCTGCGCTG TCTCTGGTGG CTCCATCAGC AGTAGAAACT GGTGGAGTTG GGTCCGCCAG
    TGGACGCGAC AGAGACCACC GAGGTAGTCG TCATCTTTGA CCACCTCAAC CCAGGCGGTC

                                                                    VH-CDR2
          P  P  G  K     G  L  E     W  I  G     D  I  Y  H     S  G  S     T  N  Y
121 CCCCCAGGGA AGGGGCTGGA GTGGATTGGT GATATCTATC ATAGTGGGAG CACCAACTAC
    GGGGGTCCCT TCCCCGACCT CACCTAACCA CTATAGATAG TATCACCCTC GTGGTTGATG

          N  P  S  L     K  S  R     V  T  I     S  V  D  K     S  K  N     Q  F  S
181 AACCCGTCCC TCAAGAGTCG AGTCACCATA TCAGTAGACA AGTCCAAGAA CCAGTTCTCC
    TTGGGCAGGG AGTTCTCAGC TCAGTGGTAT AGTCATCTGT TCAGGTTCTT GGTCAAGAGG
```

Fig. 8

```
241  L  K  L  S  S  V  T  A  A  D  T  A  V  Y  Y  C  A  S  G  Y
     CTGAAGCTGA GCTCTGTGAC CGCCGCGGAC ACGGCCGTGT ATTACTGTGC GAGTGGGTAT
     GACTTCGACT CGAGACACTG GCGGCGCCTG TGCCGGCACA TAATGACACG CTCACCCATA

     VH-CDR3
     T  S  C  R  D  A  F  D  I  W  G  Q  G  T  M  V  T  V  S  S
301  ACCAGCTGTC GTGATGCTTT TGATATCTGG GGCCAAGGGA CAATGGTCAC CGTCTCCTCA
     TGGTCGACAG CACTACGAAA ACTATAGACC CCGGTTCCCT GTTACCAGTG GCAGAGGAGT

     G  G  G  G  S  G  G  G  S  G  G  G  G  S  E  L  V  M  T
361  GGTGGTGGTG GTTCTGGCGG CGGCGGCTCC GGTGGTGGTG GTTCTGAGCT CGTGATGACT
     CCACCACCAC CAAGACCGCC GCCGCCGAGG CCACCACCAC CAAGACTCGA GCACTACTGA

     Q  S  P  S  S  L  S  A  S  V  G  D  R  V  T  I  T  C  R  A
421  CAGTCTCCAT CCTCCCTGTC TGCATCTGTA GGAGACAGAG TCACCATCAC TTGCCGGGCG
     GTCAGAGGTA GGAGGGACAG ACGTAGACAT CCTCTGTCTC AGTGGTAGTG AACGGCCCGC

     VL-CDR1
     S  Q  G  I  G  N  Y  L  A  W  Y  Q  Q  K  P  G  Q  P  P  K
481  AGTCAGGGCA TTGGCAATTA TTTAGCCTGG TATCAGCAGA AACCAGGGCA GCCTCCTAAG
     TCAGTCCCGT AACCGTTAAT AAATCGGACC ATAGTCGTCT TTGGTCCCGT CGGAGGATTC
```

Fig. 8 (cont.)

```
                                VL-CDR2
      M  L  I  Y    W  A  S    I  R  E    S  G  V  P    D  R  F    S  G  S
541   ATGCTCATTT ACTGGGCATC AATCCGGGAA TCCGGGGTCC CTGACCGATT CAGTGGCAGC
      TACGAGTAAA TGACCCGTAG TTAGGCCCTT AGGCCCCAGG GACTGGCTAA GTCACCGTCG

      G  S  G  T    D  F  T    L  T  I    S  S  L  Q    A  E  D    V  A  V
601   GGGTCTGGGA CAGACTTCAC TCTCACCATC AGCAGCCTGC AGGCTGAAGA TGTGGCAGTT
      CCCAGACCCT GTCTGAAGTG AGAGTGGTAG TCGTCGGACG TCCGACTTCT ACACCGTCAA

                                VL-CDR3
      Y  Y  C  Q    Q  Y  Y    S  N  P    Q  T  F  G    Q  G  T    K  V  E
661   TACTACTGTC AGCAATATTA TAGTAATCCT CAGACGTTCG GCCAAGGGAC CAAGGTGGAA
      ATGATGACAG TCGTTATAAT ATCATTAGGA GTCTGCAAGC CGGTTCCCTG GTTCCACCTT

      I  K
721   ATCAAA
      TAGTTT
```

Fig. 8 (cont.)

3-190

```
      E  L  Q  L  V  E  W  G  A  G  L  L  K  P  S  E  T  L  S  L
1     GAGCTGCAGC TGGTCGAGTG GGGCGCAGGA CTGTTGAAGC CTTCGGAGAC CCTGTCCCTC
      CTCGACGTCG ACCAGCTCAC CCCGCGTCCT GACAACTTCG GAAGCCTCTG GGACAGGGAG

                                        VH-CDR1
      T  C  A  V  Y  G  G  S  F  S  G  Y  Y  W  S  W  I  R  Q  P
61    ACCTGCGCTG TCTATGGTGG GTCCTTCAGT GGTTACTACT GGAGCTGGAT CCGCCAGCCC
      TGGACGCGAC AGATACCACC CAGGAAGTCA CCAATGATGA CCTCGACCTA GGCGGTCGGG

                                                          VH-CDR2
      P  G  K  G  L  E  W  I  G  E  I  N  H  S  G  S  T  N  Y  N
121   CCAGGGAAGG GGCTGGAGTG GATTGGGGAA ATCAATCATA GTGGAAGCAC CAACTACAAC
      GGTCCCTTCC CCGACCTCAC CTAACCCCTT TAGTTAGTAT CACCTTCGTG GTTGATGTTG

      P  S  L  K  S  R  V  T  I  S  V  D  T  S  K  N  Q  F  S  L
181   CCGTCCCTCA AGAGTCGAGT CACCATATCA GTAGACACGT CCAAGAACCA GTTCTCCCTG
      GGCAGGGAGT TCTCAGCTCA GTGGTATAGT CATCTGTGCA GGTTCTTGGT CAAGAGGGAC
```

Fig. 9

```
                                                                  G R G
241  K L S S V T A A D T A V Y Y C A R AGGCCGAGGC
     AAGCTGAGCT CTGTGACCGC CGCGGACACG GCTGTGTATT ACTGTGCGAG TCCGGCTCCG
     TTCGACTCGA GACACTGGCG GCGCCTGTGC CGACACATAA TGACACGCTC
                                                                  Q G T
301  R F L G W L L G G G S N W F D P W G CCAGGGAACC
     CGATTTTTGG GGTGGTTATT AGGGGGCTCC AACTGGTTCG ACCCCTGGGG GGTCCCTTGG
     GCTAAAAACC CCACCAATAA TCCCCCGAGG TTGACCAAGC TGGGGACCCC
                                                                  G G G
361  L V T V S S G G G G S G G G G S G TGGTGGTGGT
     CTGGTCACCG TCTCCTCAGG TGGTGGTGGT TCTGGCGGCG GCGGCTCCGG ACCACCACCA
     GACCAGTGGC AGAGGAGTCC ACCACCACCA AGACCGCCGC CGCCGAGGCC
                                                                  D R V
421  S E L V M T Q S P S S L S A S V G AGACAGAGTC
     TCTGAGCTCG TGATGACCCA GTCTCCATCC TCCCTGTCTG CATCTGTAGG TCTGTCTCAG
     AGACTCGAGC ACTACTGGGT CAGAGGTAGG AGGGACAGAC GTAGACATCC
                                                                  Q Q K
481  T I T C R A S Q G I S N Y L N W Y TCAGCAGAAA
     ACCATCACTT GCCGGGCGAG TCAGGGCATT AGCAATTATT TAAATTGGTA AGTCGTCTTT
     TGGTAGTGAA CGGCCCGCTC AGTCCCGTAA TCGTTAATAA ATTTAACCAT
```

VH-CDR3

VL-CDR1

Fig. 9 (cont.)

```
                                           VL-CDR2
         P  G  K  A   P  K  L   L  I  Y   D  A  S  N   L  E  T   G  V  P
541      CCAGGGAAAG CCCCTAAGCT CCTGATCTAC GATGCATCCA ATTTGGAAAC AGGGGTCCCA
         GGTCCCTTTC GGGGATTCGA GGACTAGATG CTACGTAGGT TAAACCTTTG TCCCCAGGGT

         S  R  F  S   G  S  G   S  G  T   D  F  T  L   T  I  S   S  L  Q
601      TCAAGGTTCA GTGGCAGTGG ATCTGGGACA GATTTCACTC TCACCATCAG CAGTCTGCAA
         AGTTCCAAGT CACCGTCACC TAGACCCTGT CTAAAGTGAG AGTGGTAGTC GTCAGACGTT

                                          VL-CDR3
         P  E  D  F   A  T  Y   Y  C  Q   Q  S  Y  S   T  P  Y   T  F  G
661      CCTGAAGATT TTGCAACTTA CTACTGTCAA CAGAGTTACA GTACCCCGTA CACTTTTGGC
         GGACTTCTAA AACGTTGAAT GATGACAGTT GTCTCAATGT CATGGGGCAT GTGAAAACCG

         Q  G  T  K   V  D  I   K
721      CAGGGGACCA AAGTGGATAT CAAA
         GTCCCCTGGT TTCACCTATA GTTT
```

Fig. 9 (cont.)

3-271

```
          E  L  Q  L  V  E  W     G  A  G     L  L  K  P     S  E  T     L  S  L
1   GAGCTGCAGC TGGTCGAGTG GGGCGCAGGA CTGTTGAAGC CTTCGGAGAC CCTGTCCCTC
    CTCGACGTCG ACCAGCTCAC CCCGCGTCCT GACAACTTCG GAAGCCTCTG GGACAGGGAG

                                    VH-CDR1
          T  C  A  V     Y  G  G     S  F  S     G  Y  Y  W     S  W  I     R  Q  P
61  ACCTGCGCTG TCTATGGTGG GTCCTTCAGT GGTTACTACT GGAGCTGGAT CCGCCAGCCC
    TGGACGCGAC AGATACCACC CAGGAAGTCA CCAATGATGA CCTCGACCTA GGCGGTCGGG

                                                                    VH-CDR2
          P  G  K  G     L  E  W     I  G  E     I  N  H  S     G  S  T     N  Y  N
121 CCAGGGAAGG GGCTGGAGTG GATTGGGGAA ATCAATCATA GTGGAAGCAC CAACTACAAC
    GGTCCCTTCC CCGACCTCAC CTAACCCCTT TAGTTAGTAT CACCTTCGTG GTTGATGTTG

          P  S  L  K     S  R  V     T  I  S  V  D  T  S     K  N  Q     F  S  L
181 CCGTCCCTCA AGAGTCGAGT CACCATATCA GTAGACACGT CCAAGAACCA GTTCTCCCTG
    GGCAGGGAGT TCTCAGCTCA GTGGTATAGT CATCTGTGCA GGTTCTTGGT CAAGAGGGAC
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Fig. 10

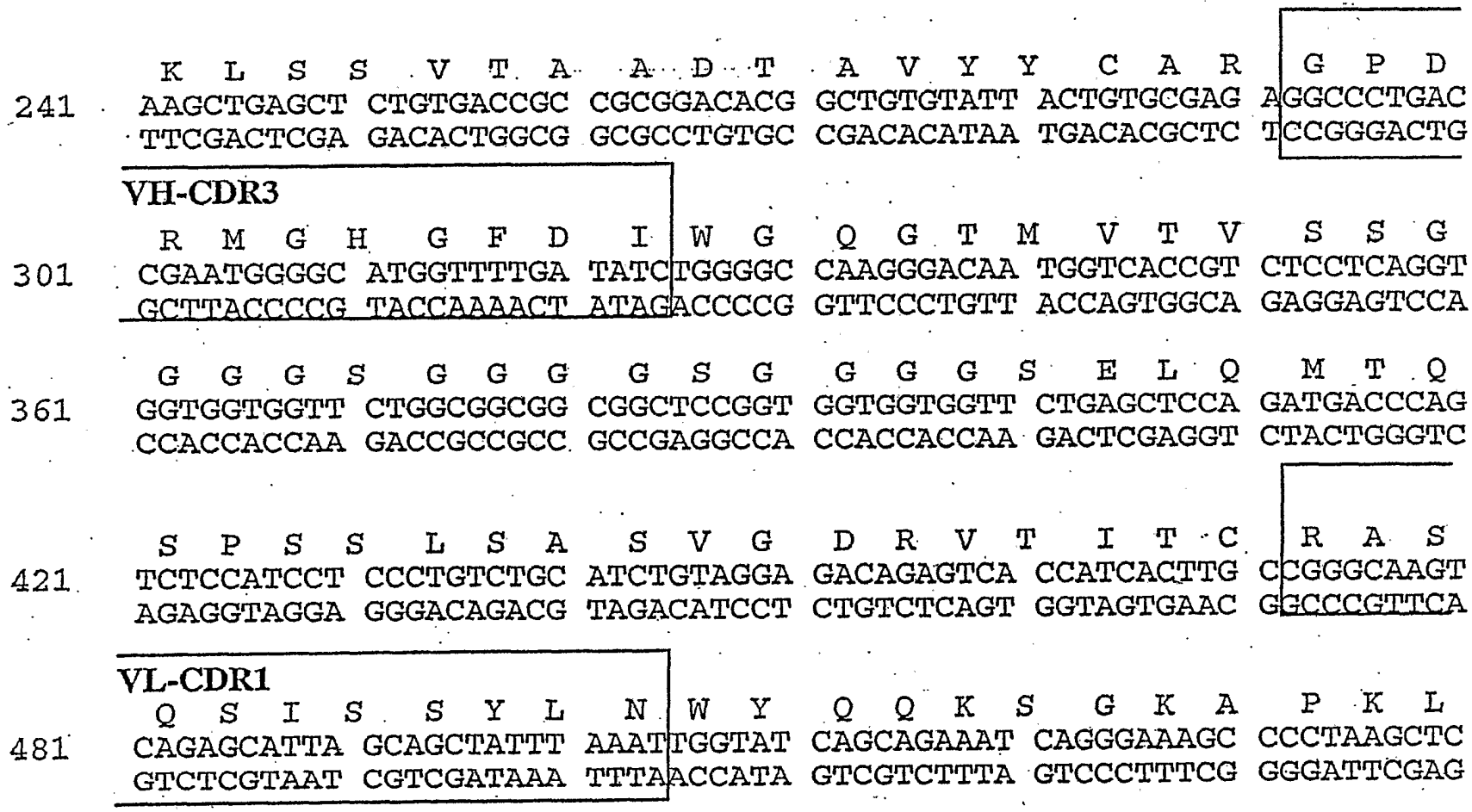

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TTCGACTCGA GACACTGGCG GCGCCTGTGC CGACACATAA TGACACGCTC TCCGGGACTG
VH-CDR3
R M G H G F D I W G Q G T M V T V S S G
301 CGAATGGGGC ATGGTTTTGA TATCTGGGGC CAAGGGACAA TGGTCACCGT CTCCTCAGGT
GCTTACCCCG TACCAAAACT ATAGACCCCG GTTCCCTGTT ACCAGTGGCA GAGGAGTCCA
G G G S G G G G S G G G G S E L Q M T Q
361 GGTGGTGGTT CTGGCGGCGG CGGCTCCGGT GGTGGTGGTT CTGAGCTCCA GATGACCCAG
CCACCACCAA GACCGCCGCC GCCGAGGCCA CCACCACCAA GACTCGAGGT CTACTGGGTC
S P S S L S A S V G D R V T I T C R A S
421 TCTCCATCCT CCCTGTCTGC ATCTGTAGGA GACAGAGTCA CCATCACTTG CCGGGCAAGT
AGAGGTAGGA GGGACAGACG TAGACATCCT CTGTCTCAGT GGTAGTGAAC GGCCCGTTCA
VL-CDR1
Q S I S S Y L N W Y Q Q K S G K A P K L
481 CAGAGCATTA GCAGCTATTT AAATTGGTAT CAGCAGAAAT CAGGGAAAGC CCCTAAGCTC
GTCTCGTAAT CGTCGATAAA TTTAACCATA GTCGTCTTTA GTCCCTTTCG GGGATTCGAG

Fig. 10 (cont.)

```
                                  VL-CDR2
          L  I  Y  A  A  S  S  L  Q  S   G  V  P  S  R  F  S  G  S  G
541  CTGATCTATG CTGCATCCAG TTTGCAAAGT GGGGTCCCAT CAAGGTTCAG TGGCAGTGGA
     GACTAGATAC GACGTAGGTC AAACGTTTCA CCCCAGGGTA GTTCCAAGTC ACCGTCACCT

          S  G  T  D  F  T  L  T  I  S   S  L  Q  P  E  D  F  A  T  Y
601  TCTGGGACAG ATTTCACTCT CACCATCAGT AGTCTGCAAC CTGAAGATTT TGCAACTTAT
     AGACCCTGTC TAAAGTGAGA GTGGTAGTCA TCAGACGTTG GACTTCTAAA ACGTTGAATA

                               VL-CDR3
          Y  C  Q  Q  S  Y  S  S  P  W   T  F  G  Q  G  T  K  V  E  I
661  TACTGTCAAC AGAGTTACAG TAGCCCGTGG ACATTCGGCC AAGGGACCAA GGTGGAGATC
     ATGACAGTTG TCTCAATGTC ATCGGGCACC TGTAAGCCGG TTCCCTGGTT CCACCTCTAG

          K
721  AAA
     TTT
```

Fig. 10 (cont.)

3-550

```
      E  L  Q  L     V  E  S     G  P  G     L  V  K  P     S  Q  T     L  S  L
1     GAGCTGCAGC TGGTCGAGTC TGGTCCAGGA CTGGTGAAGC CCTCGCAGAC CCTCTCACTC
      CTCGACGTCG ACCAGCTCAG ACCAGGTCCT GACCACTTCG GGAGCGTCTG GGAGAGTGAG

                                                  VH-CDR1
      T  C  A  I     S  G  D     S  V  S     S  N  S  A     A  W  N     W  I  R
61    ACCTGTGCCA TCTCCGGGGA CAGTGTCTCT AGCAACAGTG CTGCTTGGAA CTGGATCAGG
      TGGACACGGT AGAGGCCCCT GTCACAGAGA TCGTTGTCAC GACGAACCTT GACCTAGTCC

                                                                  VH-CDR2
      Q  S  P  S     R  G  L     E  W  L     G  R  T  Y     Y  R  S     K  W  Y
121   CAGTCCCCAT CGAGAGGCCT TGAGTGGCTG GGAAGGACAT ACTACAGGTC CAAGTGGTAT
      GTCAGGGGTA GCTCTCCGGA ACTCACCGAC CCTTCCTGTA TGATGTCCAG GTTCACCATA

      N  D  Y  A     V  S  V     K  S  R     I  T  I  N     P  D  T     S  K  N
181   AATGATTATG CAGTATCTGT GAAAAGTCGA ATAACCATCA ACCCAGACAC ATCCAAGAAC
      TTACTAATAC GTCATAGACA CTTTTCAGCT TATTGGTAGT TGGGTCTGTG TAGGTTCTTG
```

Fig. 11

```
          Q  F  S  L  Q  L  N  S  V  T  P  E  D  T  A  V  Y  Y  C  A
241  CAGTTCTCCC TGCAGCTGAA CTCTGTGACT CCCGAGGACA CGGCTGTGTA TTACTGTGCA
     GTCAAGAGGG ACGTCGACTT GAGACACTGA GGGCTCCTGT GCCGACACAT AATGACACGT

                              VH-CDR3
          R  D  R  R  R  R  I  A  A  R  Q  Y  Y  G  M  D  V  W  G  Q  G
301  AGAGATCGTC GACGTATAGC AGCTCGTCAA TACTACGGTA TGGACGTCTG GGGCCAAGGG
     TCTCTAGCAG CTGCATATCG TCGAGCAGTT ATGATGCCAT ACCTGCAGAC CCCGGTTCCC

          T  T  V  T  V  S  S  G  G  G  G  S  G  G  G  S  G  G  G
361  ACCACGGTCA CCGTCTCCTC AGGTGGTGGT GGTTCTGGCG GCGGCGGCTC CGGTGGTGGT
     TGGTGCCAGT GGCAGAGGAG TCCACCACCA CCAAGACCGC CGCCGCCGAG GCCACCACCA

          G  S  E  L  V  L  T  Q  S  P  G  T  L  S  L  S  P  G  E  R
421  GGTTCTGAGC TCGTGTTGAC ACAGTCTCCA GGCACCCTGT CTTTGTCTCC AGGGGAAAGA
     CCAAGACTCG AGCACAACTG TGTCAGAGGT CCGTGGGACA GAAACAGAGG TCCCCTTTCT

                              VL-CDR1
          A  T  L  S  C  R  A  S  Q  S  V  S  S  N  Y  L  A  W  Y  Q
481  GCCACCCTCT CCTGCAGGGC AAGTCAGAGT GTTAGCAGCA ACTACTTAGC CTGGTACCAG
     CGGTGGGAGA GGACGTCCCG TTCAGTCTCA CAATCGTCGT TGATGAATCG GACCATGGTC
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Fig. 11 (cont.)

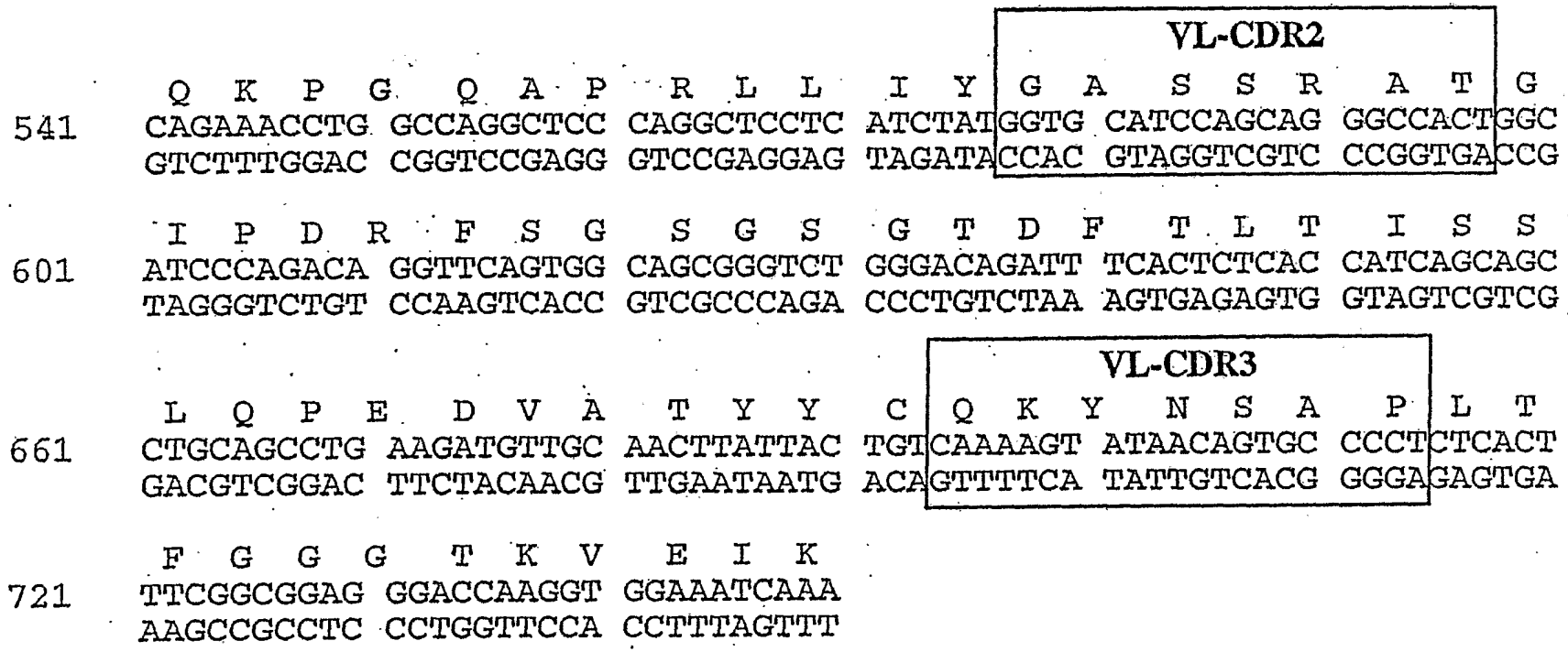

VL-CDR2
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GTCTTTGGAC CGGTCCGAGG GTCCGAGGAG TAGATACCAC GTAGGTCGTC CCGGTGACCG
I P D R F S G S G S G T D F T L T I S S
601 ATCCCAGACA GGTTCAGTGG CAGCGGGTCT GGGACAGATT TCACTCTCAC CATCAGCAGC
TAGGGTCTGT CCAAGTCACC GTCGCCCAGA CCCTGTCTAA AGTGAGAGTG GTAGTCGTCG
VL-CDR3
L Q P E D V A T Y Y C Q K Y N S A P L T
661 CTGCAGCCTG AAGATGTTGC AACTTATTAC TGTCAAAAGT ATAACAGTGC CCCTCTCACT
GACGTCGGAC TTCTACAACG TTGAATAATG ACAGTTTTCA TATTGTCACG GGGAGAGTGA
F G G G T K V E I K
721 TTCGGCGGAG GGACCAAGGT GGAAATCAAA
AAGCCGCCTC CCTGGTTCCA CCTTTAGTTT

Fig. 11 (cont.)

4-10

```
                E  L  Q  L  V  E  S     G  G  G     L  V  Q  P     G  G  S     L  R  L
    1   GAGCTGCAGC TGGTCGAGTC TGGGGGAGGC TTGGTACAGC CTGGGGGGTC CCTGAGACTC
        CTCGACGTCG ACCAGCTCAG ACCCCCTCCG AACCATGTCG GACCCCCCAG GGACTCTGAG

                                                VH-CDR1
                S  C  A  A     S  G  F     T  F  S     S  Y  A  M     G  W  V     R  Q  A
   61   TCCTGTGCAG CCTCTGGATT CACCTTTAGC AGCTATGCCA TGGGCTGGGT CCGCCAGGCT
        AGGACACGTC GGAGACCTAA GTGGAAATCG TCGATACGGT ACCCGACCCA GGCGGTCCGA

                                                                        VH-CDR2
                P  G  K  G     L  E  W     V  S     A     V  S  G  S     G  G  S     T  Y  Y
  121   CCAGGGAAGG GGCTGGAGTG GGTCTCAGCT GTTAGTGGTA GTGGTGGTAG CACATACTAC
        GGTCCCTTCC CCGACCTCAC CCAGAGTCGA CAATCACCAT CACCACCATC GTGTATGATG

                A  D  S  V     K  G     R     F  T  I     S  R  D  N     S  K  N     T  L  Y
  181   GCAGACTCCG TGAAGGGCCG GTTCACCATC TCCAGAGACA ATTCCAAGAA CACGCTGTAT
        CGTCTGAGGC ACTTCCCGGC CAAGTGGTAG AGGTCTCTGT TAAGGTTCTT GTGCGACATA
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Fig. 12

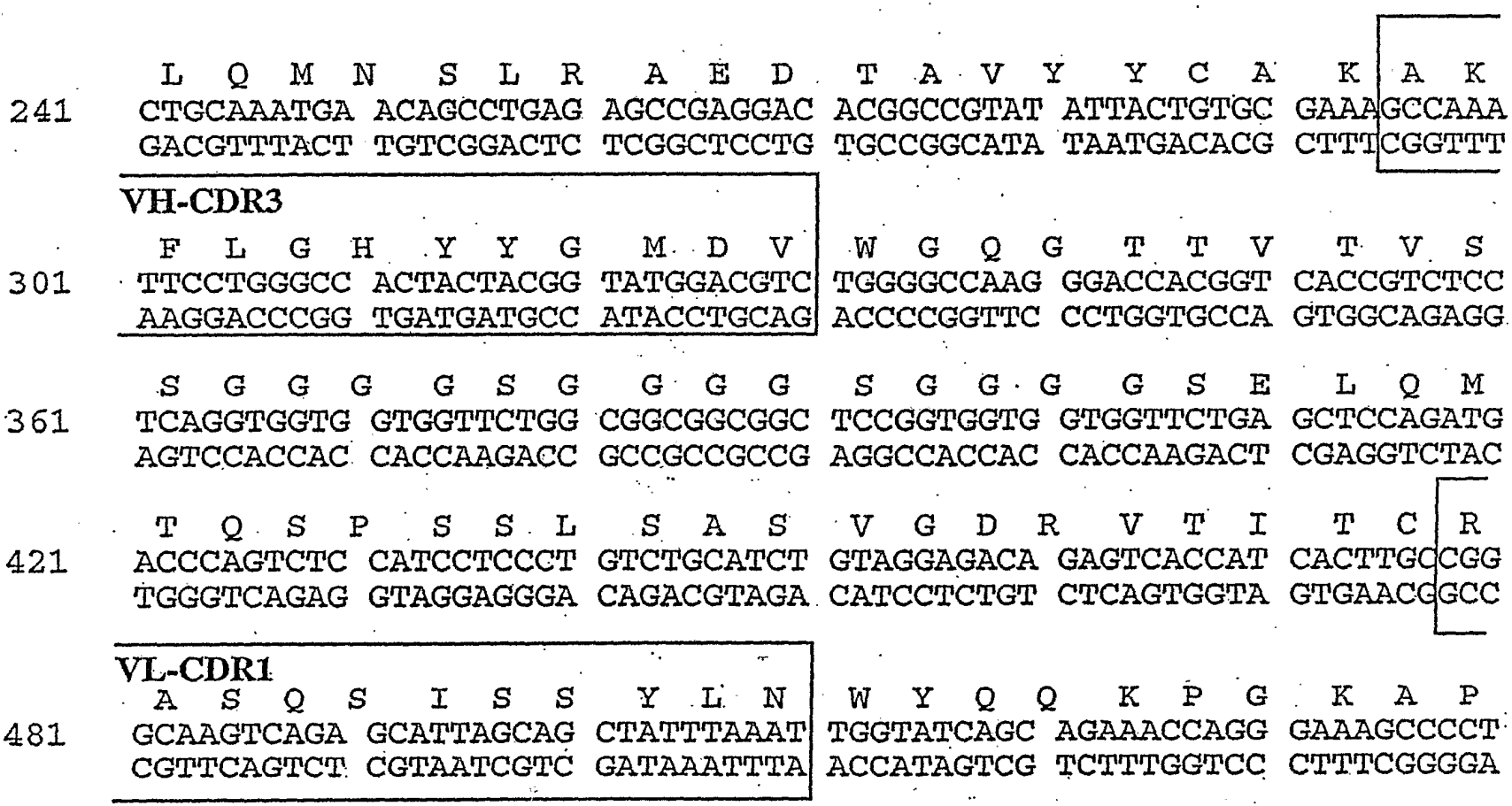

L Q M N S L R A E D T A V Y Y C A K A K
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GACGTTTACT TGTCGGACTC TCGGCTCCTG TGCCGGCATA TAATGACACG CTTTCGGTTT
VH-CDR3
F L G H Y Y G M D V W G Q G T T V T V S
301 TTCCTGGGCC ACTACTACGG TATGGACGTC TGGGGCCAAG GGACCACGGT CACCGTCTCC
AAGGACCCGG TGATGATGCC ATACCTGCAG ACCCCGGTTC CCTGGTGCCA GTGGCAGAGG
S G G G G S G G G G S G G G G S E L Q M
361 TCAGGTGGTG GTGGTTCTGG CGGCGGCGGC TCCGGTGGTG GTGGTTCTGA GCTCCAGATG
AGTCCACCAC CACCAAGACC GCCGCCGCCG AGGCCACCAC CACCAAGACT CGAGGTCTAC
T Q S P S S L S A S V G D R V T I T C R
421 ACCCAGTCTC CATCCTCCCT GTCTGCATCT GTAGGAGACA GAGTCACCAT CACTTGCCGG
TGGGTCAGAG GTAGGAGGGA CAGACGTAGA CATCCTCTGT CTCAGTGGTA GTGAACGGCC
VL-CDR1
A S Q S I S S Y L N W Y Q Q K P G K A P
481 GCAAGTCAGA GCATTAGCAG CTATTTAAAT TGGTATCAGC AGAAACCAGG GAAAGCCCCT
CGTTCAGTCT CGTAATCGTC GATAAATTTA ACCATAGTCG TCTTTGGTCC CTTTCGGGGA

Fig. 12 (cont.)

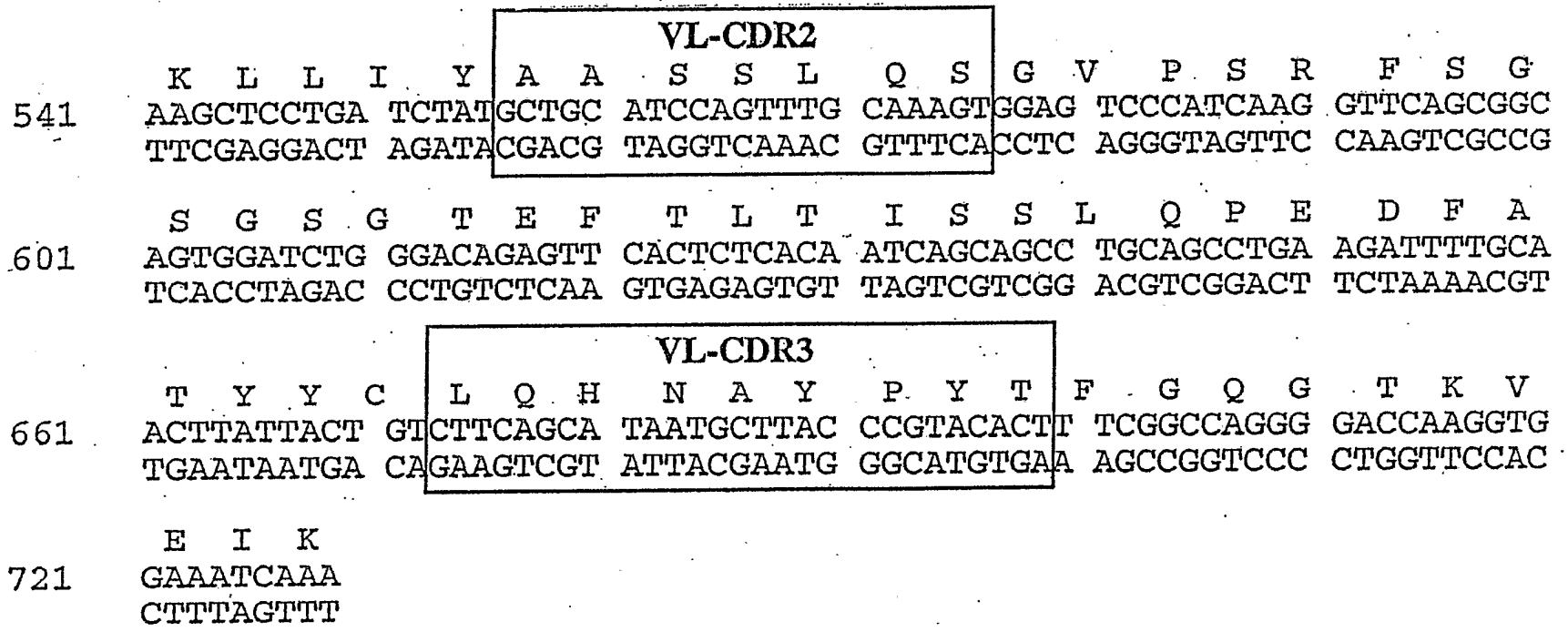

VL-CDR2
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TTCGAGGACT AGATACGACG TAGGTCAAAC GTTTCACCTC AGGGTAGTTC CAAGTCGCCG
S G S G T E F T L T I S S L Q P E D F A
601 AGTGGATCTG GGACAGAGTT CACTCTCACA ATCAGCAGCC TGCAGCCTGA AGATTTTGCA
TCACCTAGAC CCTGTCTCAA GTGAGAGTGT TAGTCGTCGG ACGTCGGACT TCTAAAACGT
VL-CDR3
T Y Y C L Q H N A Y P Y T F G Q G T K V
661 ACTTATTACT GTCTTCAGCA TAATGCTTAC CCGTACACTT TCGGCCAGGG GACCAAGGTG
TGAATAATGA CAGAAGTCGT ATTACGAATG GGCATGTGAA AGCCGGTCCC CTGGTTCCAC
E I K
721 GAAATCAAA
CTTTAGTTT

Fig. 12 (cont.)

```
                                                                VH-CDR1
      E  L  Q  L  V  E  S     G  P  V     L  V  K  P     T  D  T     L  T  L
1     GAGCTGCAGC TGGTCGAGTC TGGTCCTGTG CTGGTGAAAC CCACAGATAC CCTCACGCTG
      CTCGACGTCG ACCAGCTCAG ACCAGGACAC GACCACTTTG GGTGTCTATG GGAGTGCGAC

      T  C  T  V     S  G  F     S  L  N     N  P  R  M     G  V  S     W  I  R
61    ACTTGCACCG TCTCTGGGTT CTCACTCAAT AATCCTAGAA TGGGTGTGAG CTGGATCCGT
      TGAACGTGGC AGAGACCCAA GAGTGAGTTA TTAGGATCTT ACCCACACTC GACCTAGGCA

                                                                VH-CDR2
      Q  P  P  G     K  T  L     E  W  L     A  H  I  F     P  S  D     A  K  A
121   CAGCCCCCAG GGAAGACCCT GGAGTGGCTT GCACACATTT TTCCGAGTGA CGCAAAAGCC
      GTCGGGGGTC CCTTCTGGGA CCTCACCGAA CGTGTGTAAA AAGGCTCACT GCGTTTTCGG

      H  S  A  S     L  K  S     R  L  T     I  S  K  D     T  S  K     S  Q  V
181   CACAGTGCAT CTCTGAAGAG CAGGCTCACC ATCTCCAAGG ACACCTCCAA AAGCCAGGTG
      GTGTCACGTA GAGACTTCTC GTCCGAGTGG TAGAGGTTCC TGTGGAGGTT TTCGGTCCAC
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Fig. 13

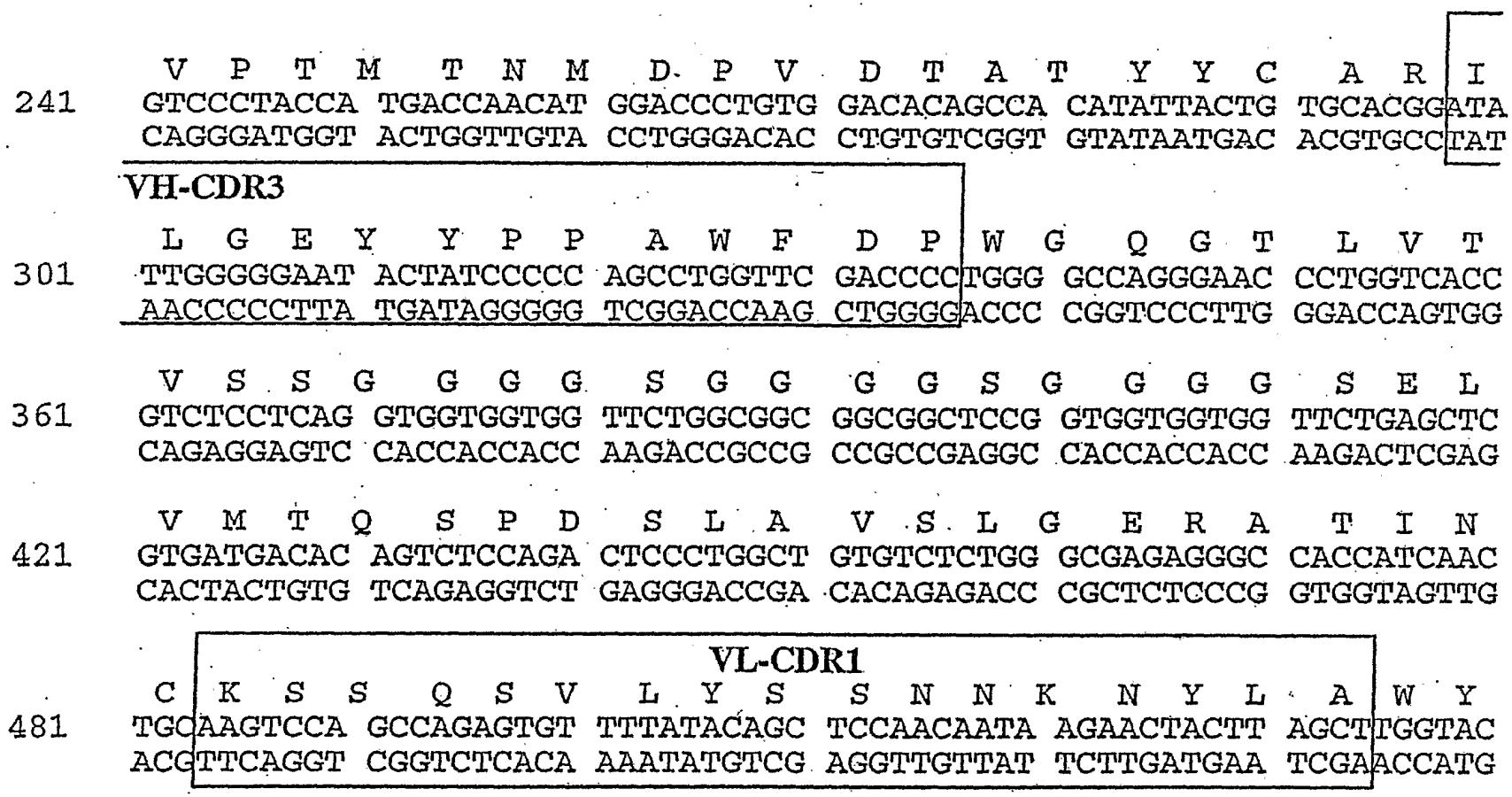

V P T M T N M D P V D T A T Y Y C A R I
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CAGGGATGGT ACTGGTTGTA CCTGGGACAC CTGTGTCGGT GTATAATGAC ACGTGCCTAT
VH-CDR3
L G E Y Y P P A W F D P W G Q G T L V T
301 TTGGGGGAAT ACTATCCCCC AGCCTGGTTC GACCCCTGGG GCCAGGGAAC CCTGGTCACC
AACCCCCTTA TGATAGGGGG TCGGACCAAG CTGGGGACCC CGGTCCCTTG GGACCAGTGG
V S S G G G G S G G G G S G G G S E L
361 GTCTCCTCAG GTGGTGGTGG TTCTGGCGGC GGCGGCTCCG GTGGTGGTGG TTCTGAGCTC
CAGAGGAGTC CACCACCACC AAGACCGCCG CCGCCGAGGC CACCACCACC AAGACTCGAG
V M T Q S P D S L A V S L G E R A T I N
421 GTGATGACAC AGTCTCCAGA CTCCCTGGCT GTGTCTCTGG GCGAGAGGGC CACCATCAAC
CACTACTGTG TCAGAGGTCT GAGGGACCGA CACAGAGACC CGCTCTCCCG GTGGTAGTTG
VL-CDR1
C K S S Q S V L Y S S N N K N Y L A W Y
481 TGCAAGTCCA GCCAGAGTGT TTTATACAGC TCCAACAATA AGAACTACTT AGCTTGGTAC
ACGTTCAGGT CGGTCTCACA AAATATGTCG AGGTTGTTAT TCTTGATGAA TCGAACCATG

Fig. 13 (cont.)

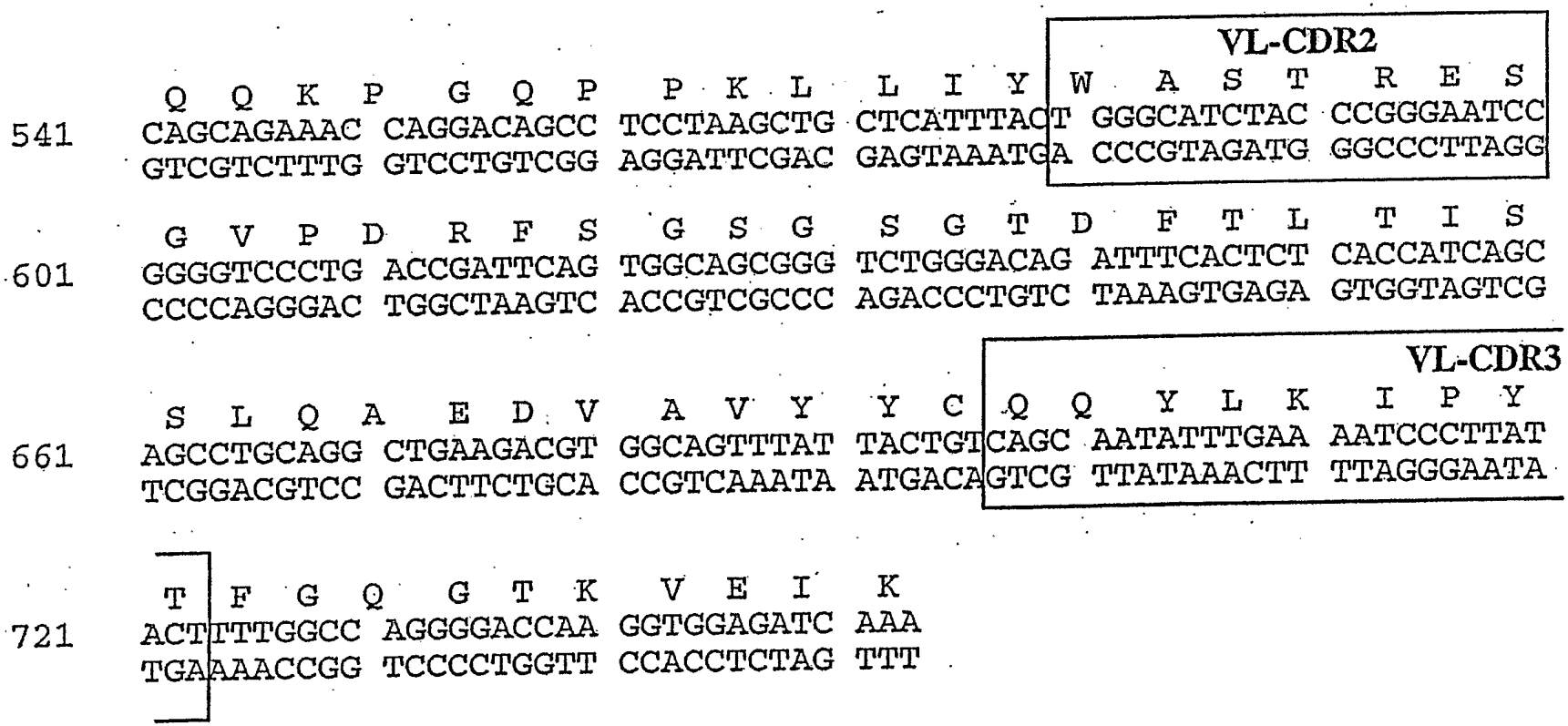

VL-CDR2
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GTCGTCTTTG GTCCTGTCGG AGGATTCGAC GAGTAAATGA CCCGTAGATG GGCCCTTAGG
G V P D R F S G S G S G T D F T L T I S
601 GGGGTCCCTG ACCGATTCAG TGGCAGCGGG TCTGGGACAG ATTTCACTCT CACCATCAGC
CCCCAGGGAC TGGCTAAGTC ACCGTCGCCC AGACCCTGTC TAAAGTGAGA GTGGTAGTCG
VL-CDR3
S L Q A E D V A V Y Y C Q Q Y L K I P Y
661 AGCCTGCAGG CTGAAGACGT GGCAGTTTAT TACTGTCAGC AATATTTGAA AATCCCTTAT
TCGGACGTCC GACTTCTGCA CCGTCAAATA ATGACAGTCG TTATAAACTT TTAGGGAATA
T F G Q G T K V E I K
721 ACTTTTGGCC AGGGGACCAA GGTGGAGATC AAA
TGAAAACCGG TCCCCTGGTT CCACCTCTAG TTT

Fig. 13 (cont.)

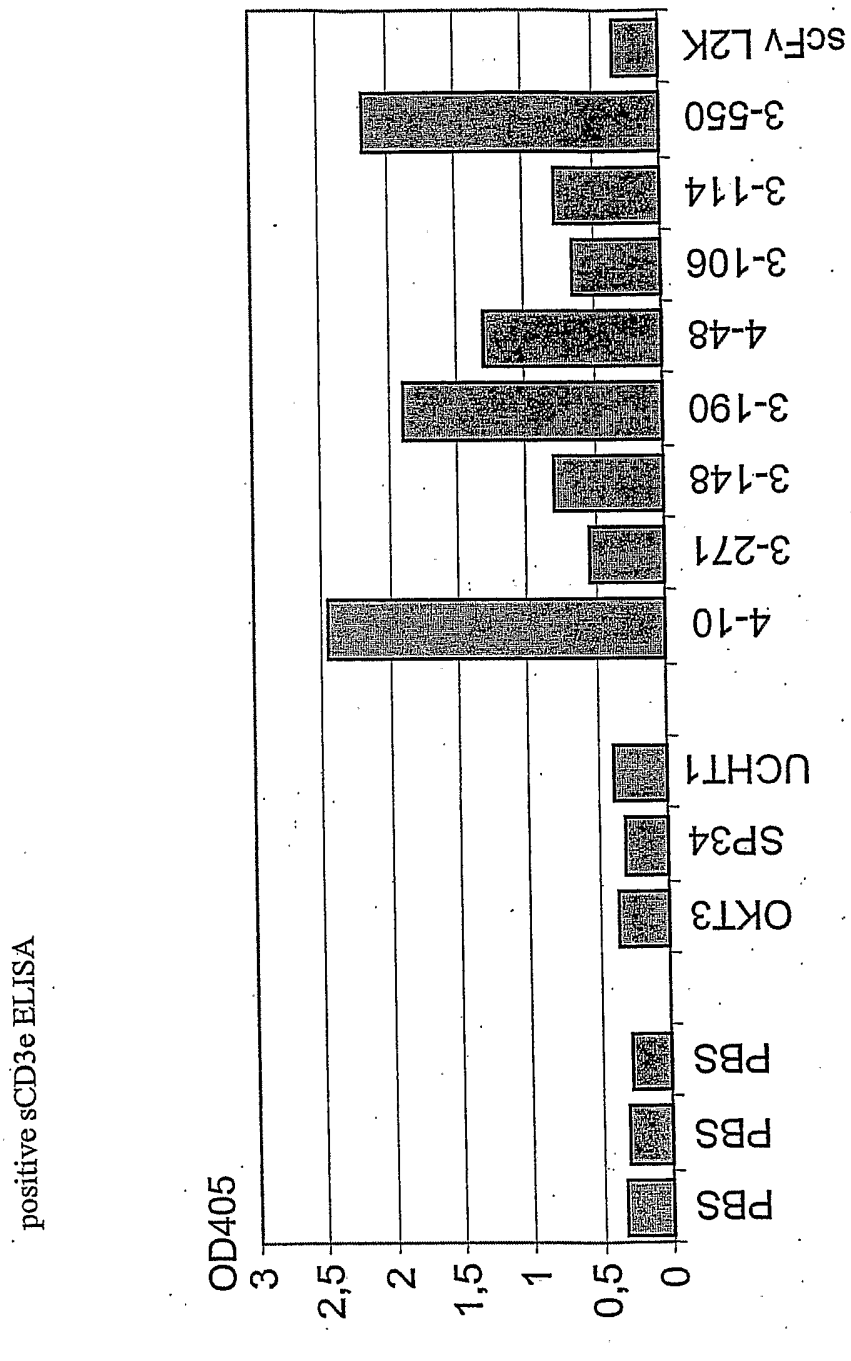

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2
1,5
1
0,5
0
PBS
PBS
PBS
OKT3
SP34
UCHT1
4-10
3-271
3-148
3-190
4-48
3-106
3-114
3-550
scFv L2K
clones

Fig. 14

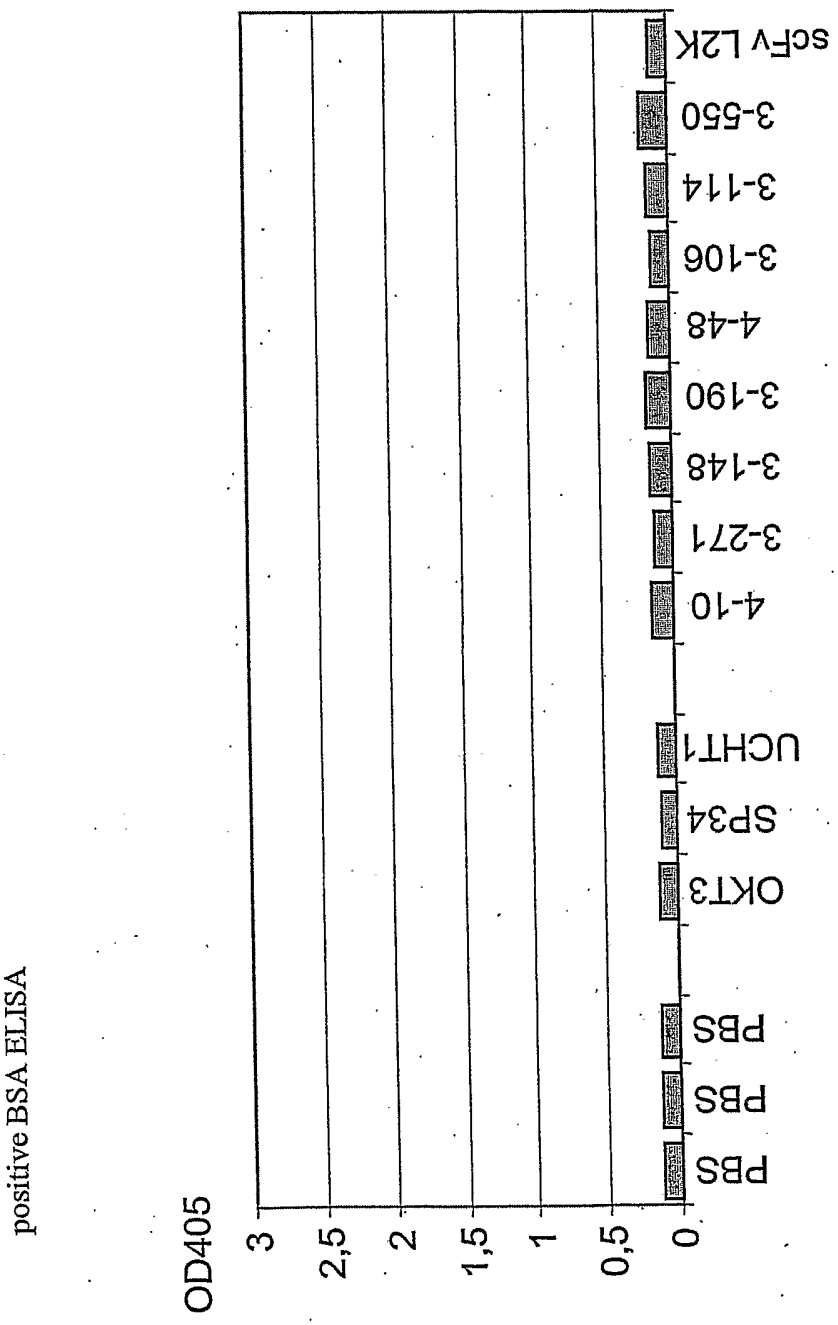

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0,5
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PBS
PBS
OKT3
SP34
UCHT1
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3-271
3-148
3-190
4-48
3-106
3-114
3-550
scFv L2K
clones

Fig. 15

Fig. 16

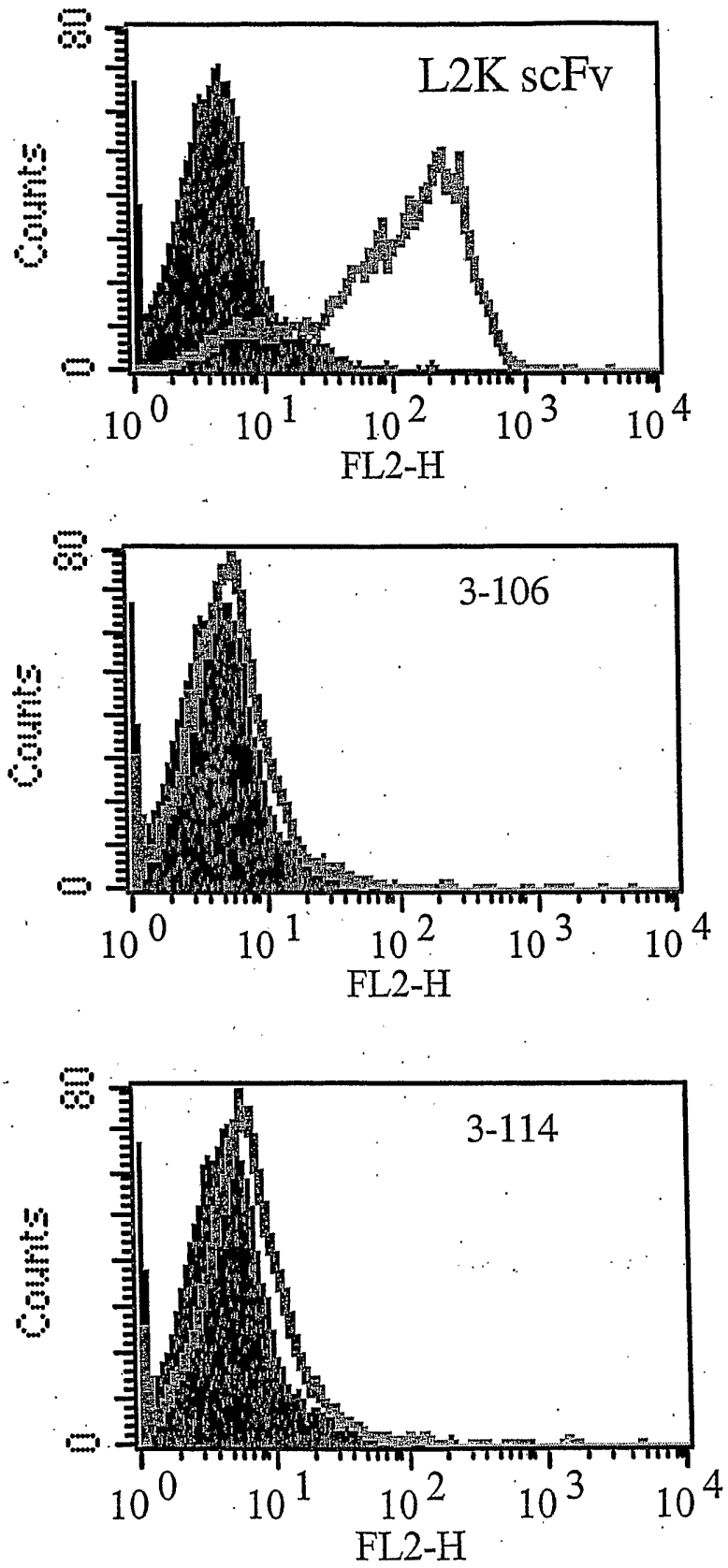


Fig. 16 (cont.) Jurkat

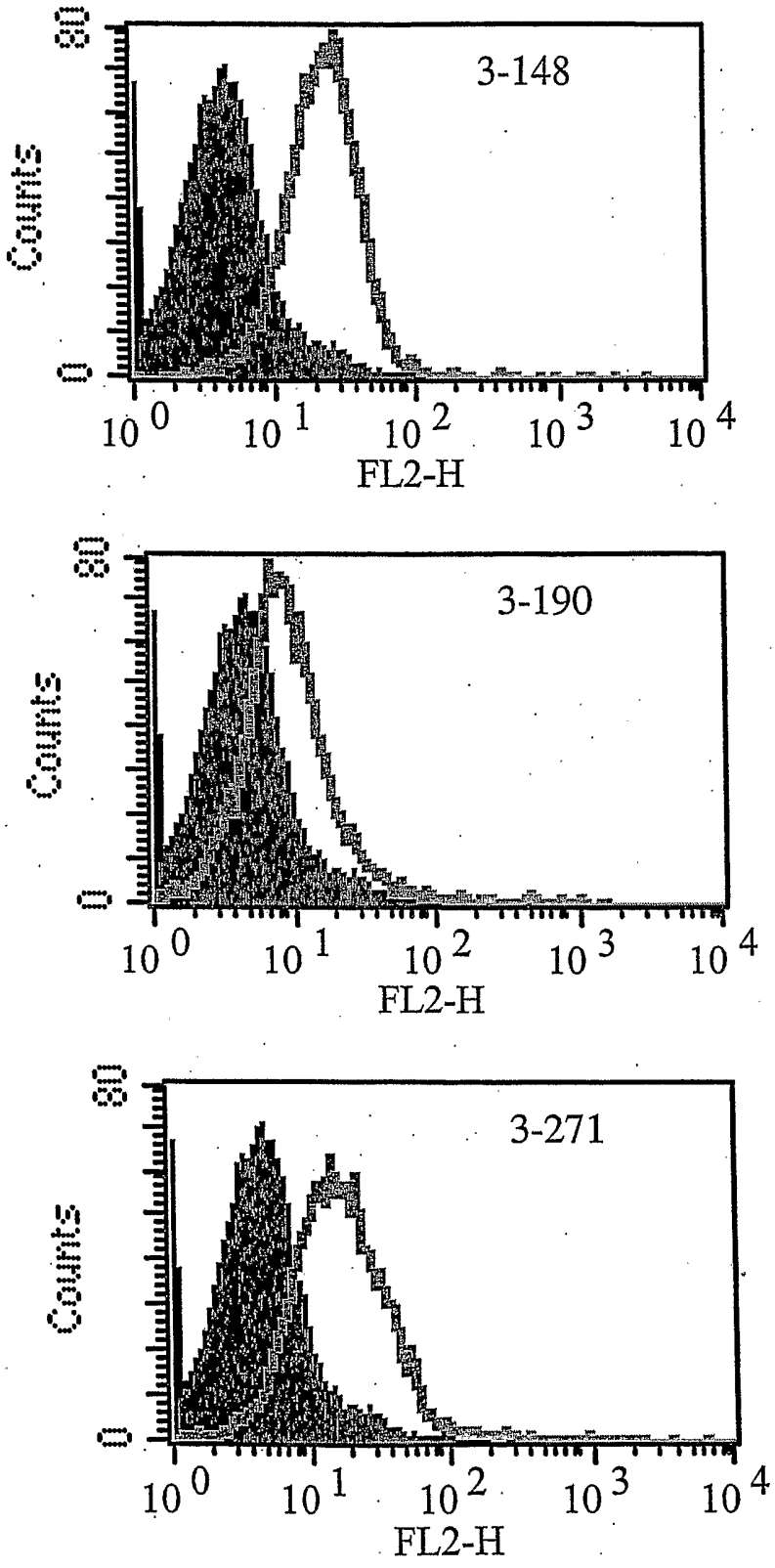


Fig. 16 (cont.) Jurkat

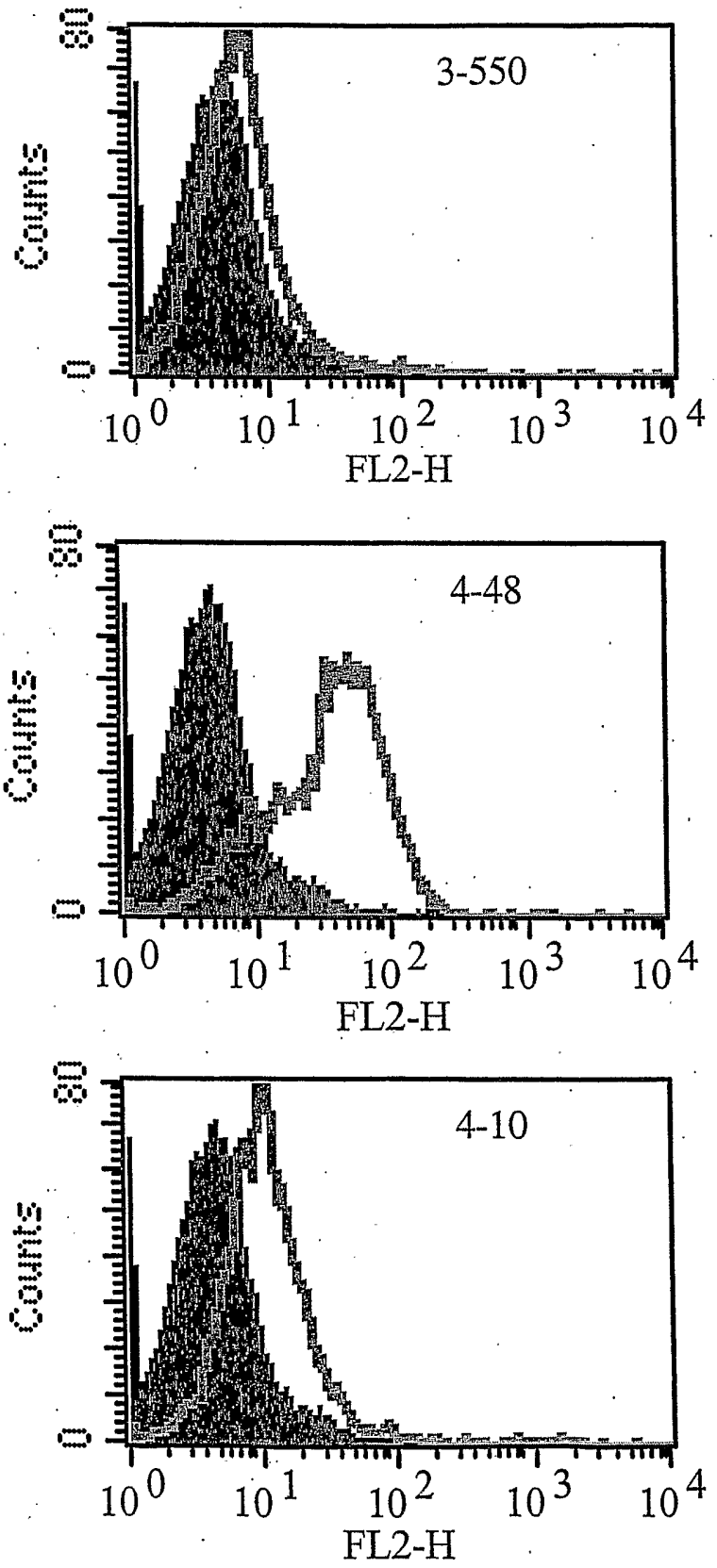
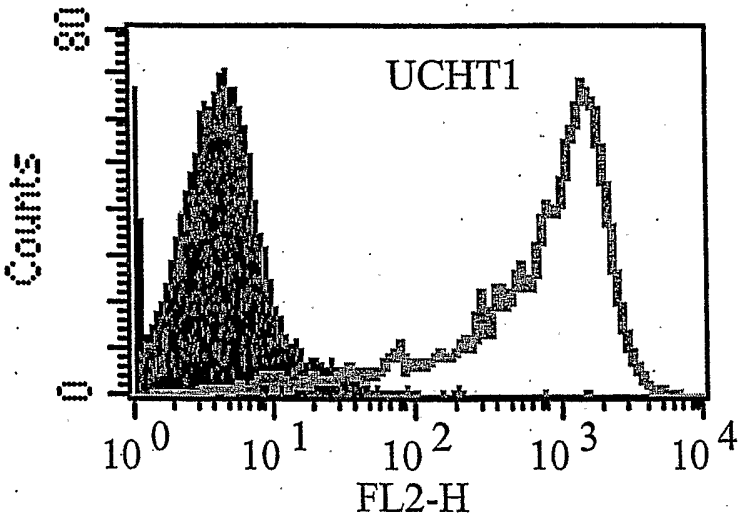
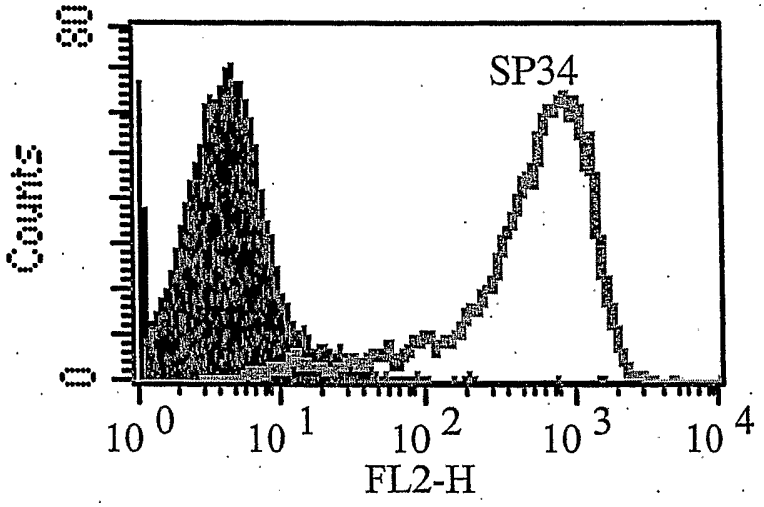


Fig. 16 (cont.) Jurkat





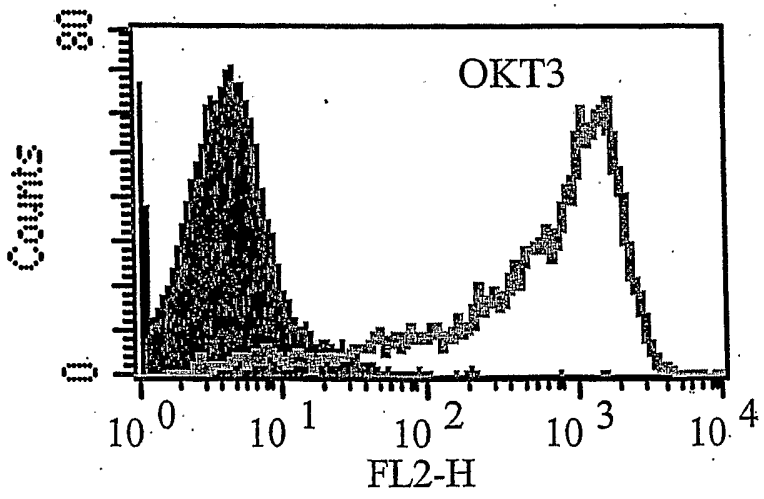


Fig. 17 CHO

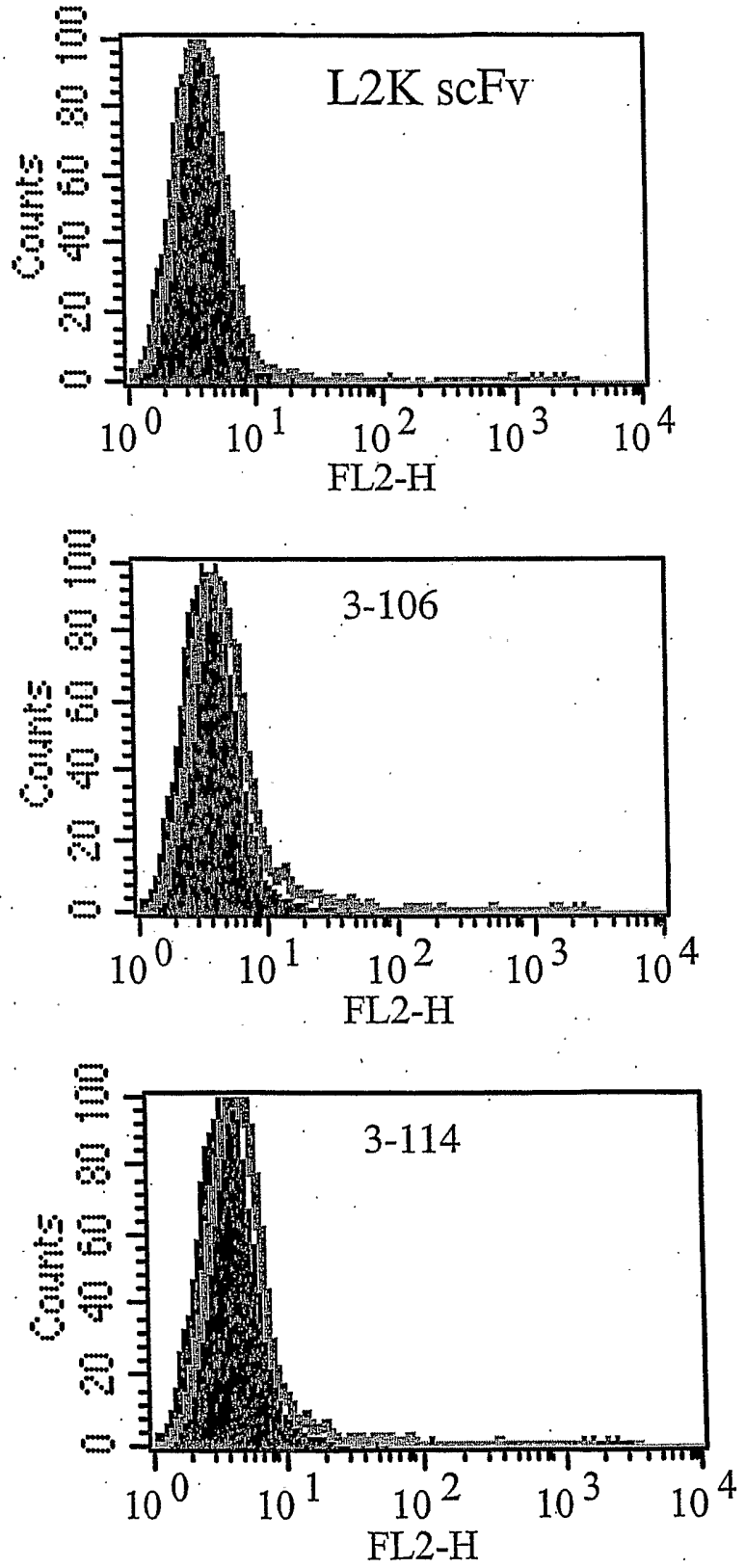

L2K scFv
3-106
3-114
Counts
0 20 40 60 80 100
10^0 10^1 10^2 10^3 10^4
FL2-H

Fig. 17 (cont.) CHO

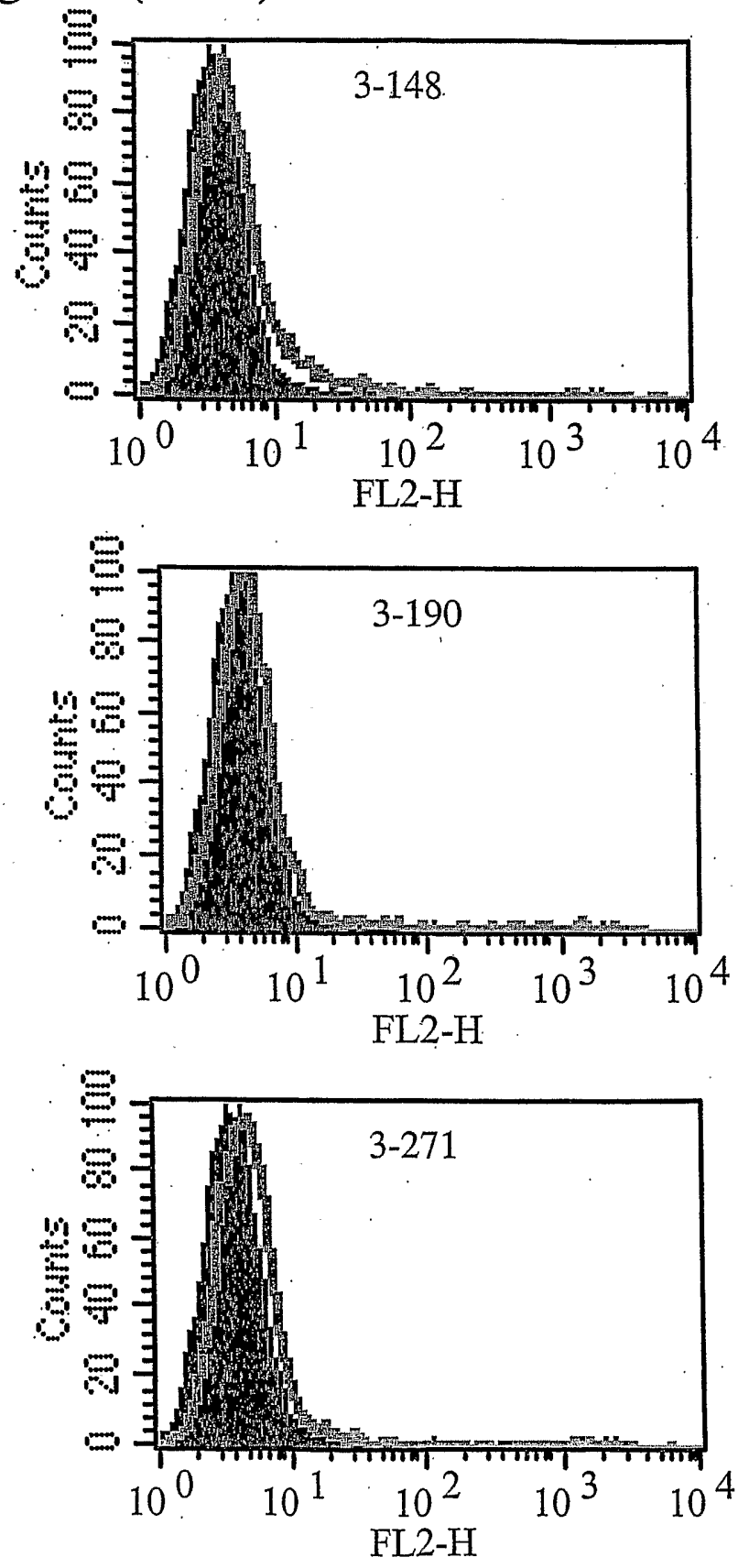


Fig. 17 (cont.) CHO

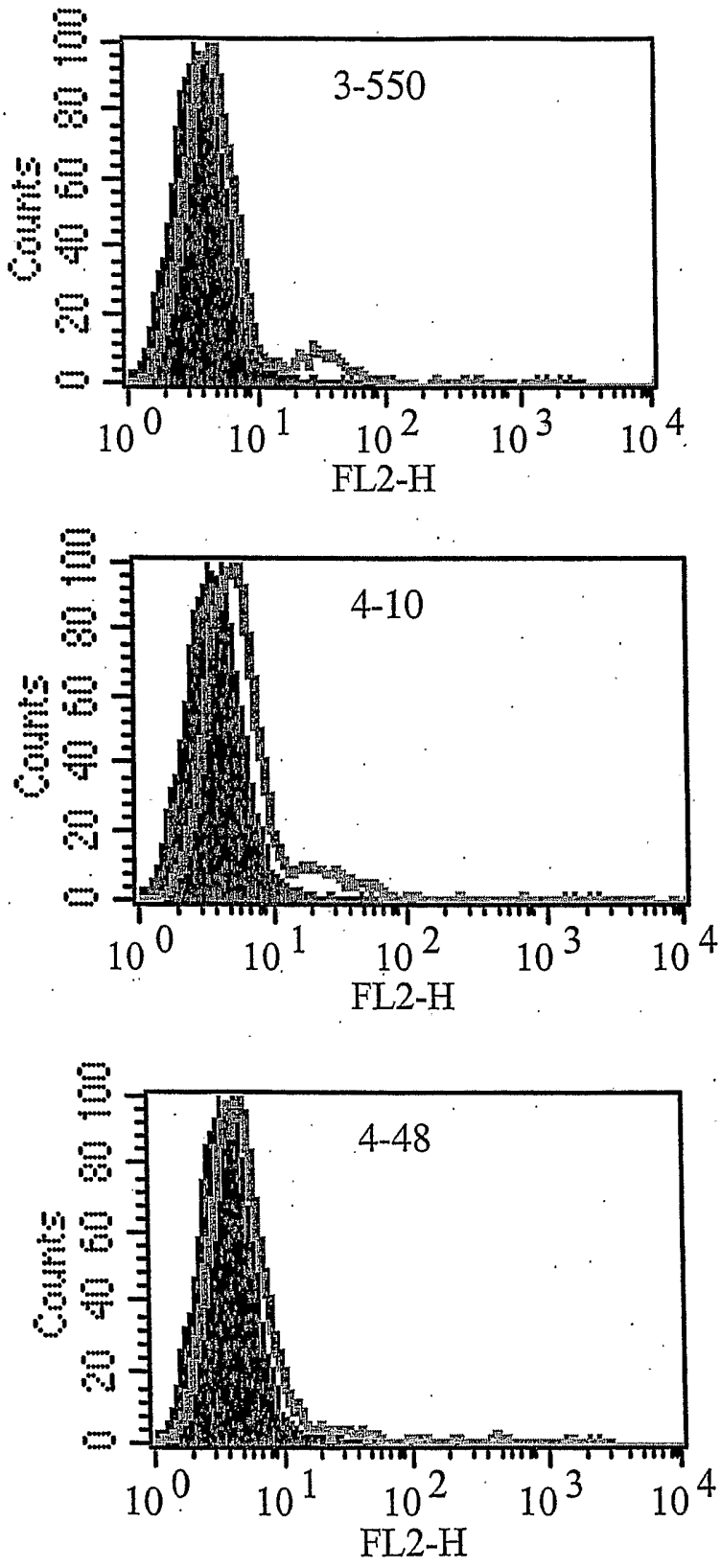


Fig. 17 (cont.) CHO

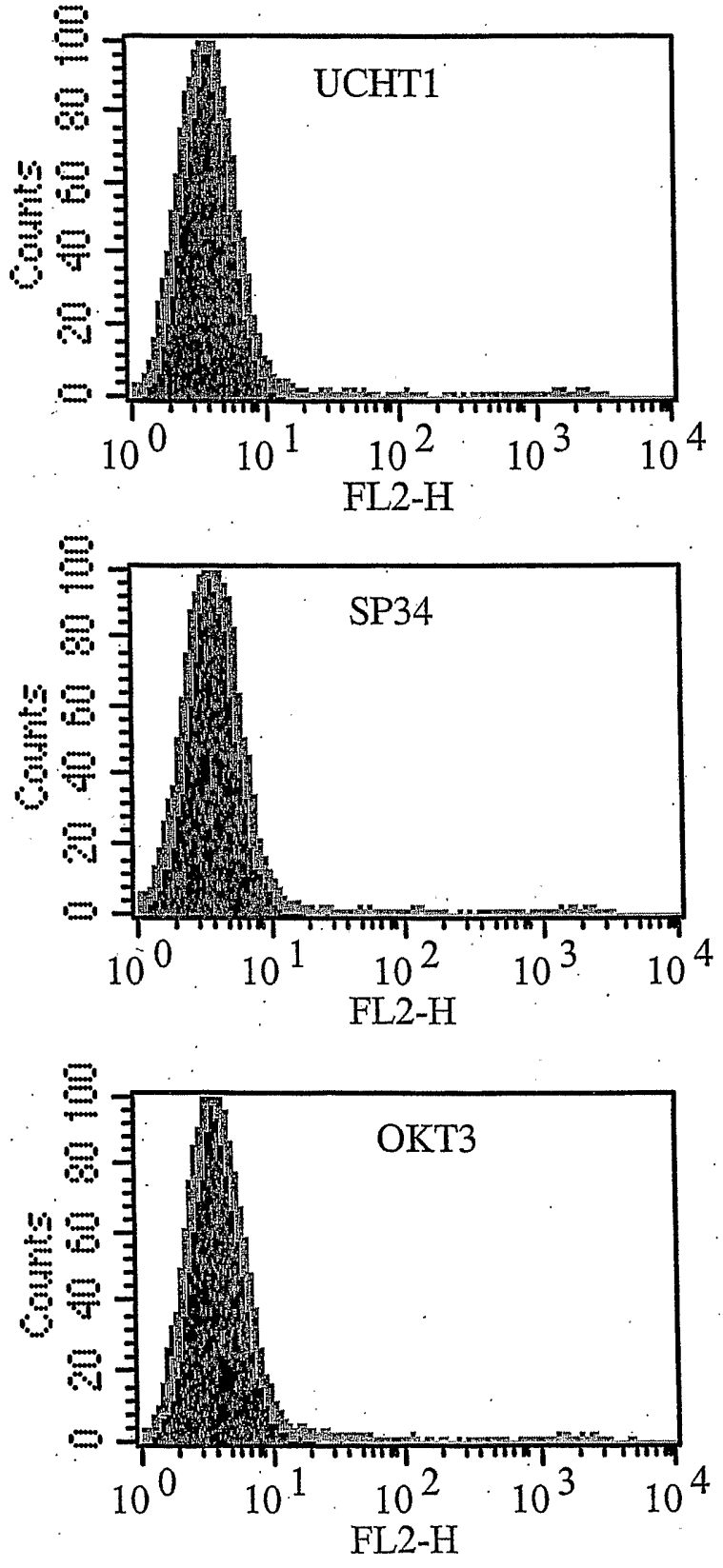


Fig. 18

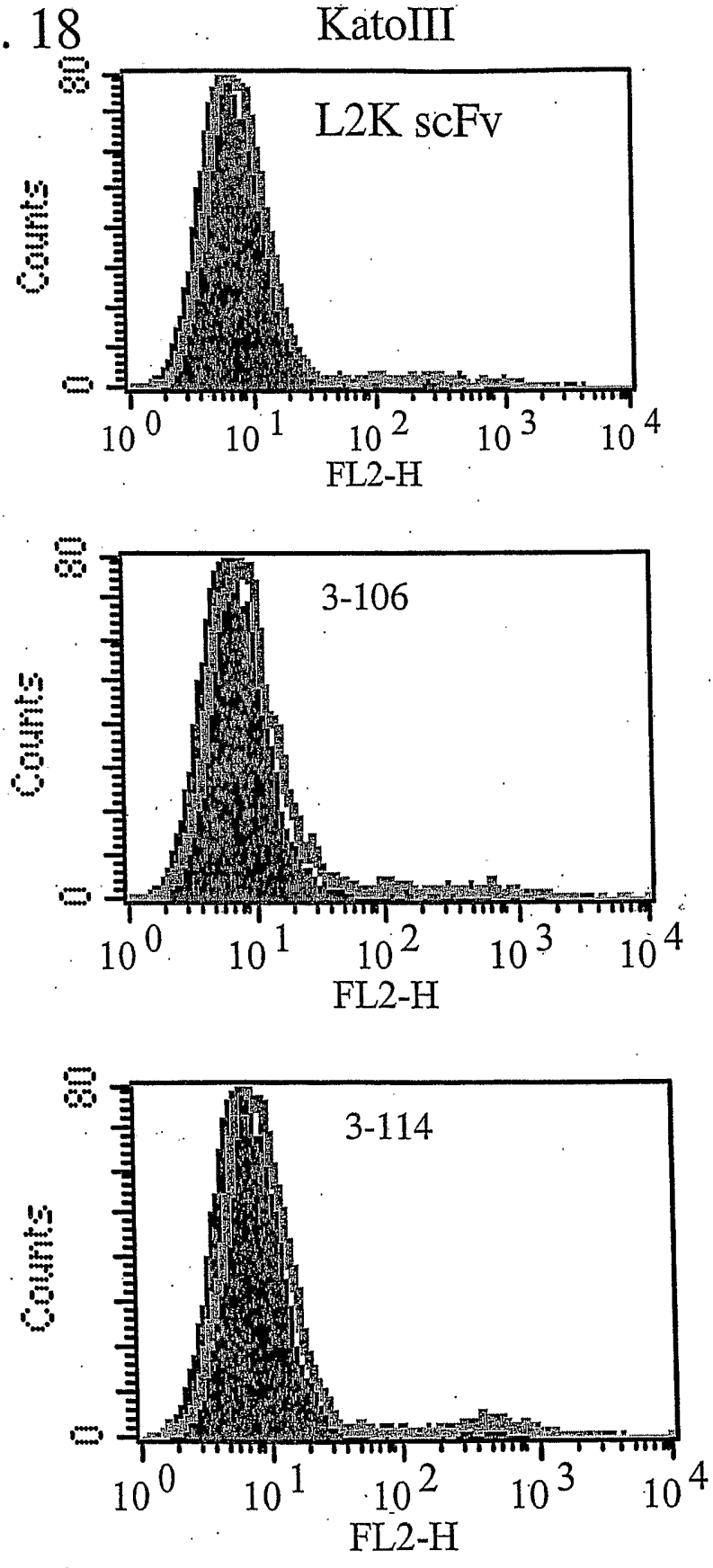

KatoIII
L2K scFv
3-106
3-114
Counts
80
0
10^0
10^1
10^2
10^3
10^4
FL2-H

Fig. 18 (cont.) KatoIII

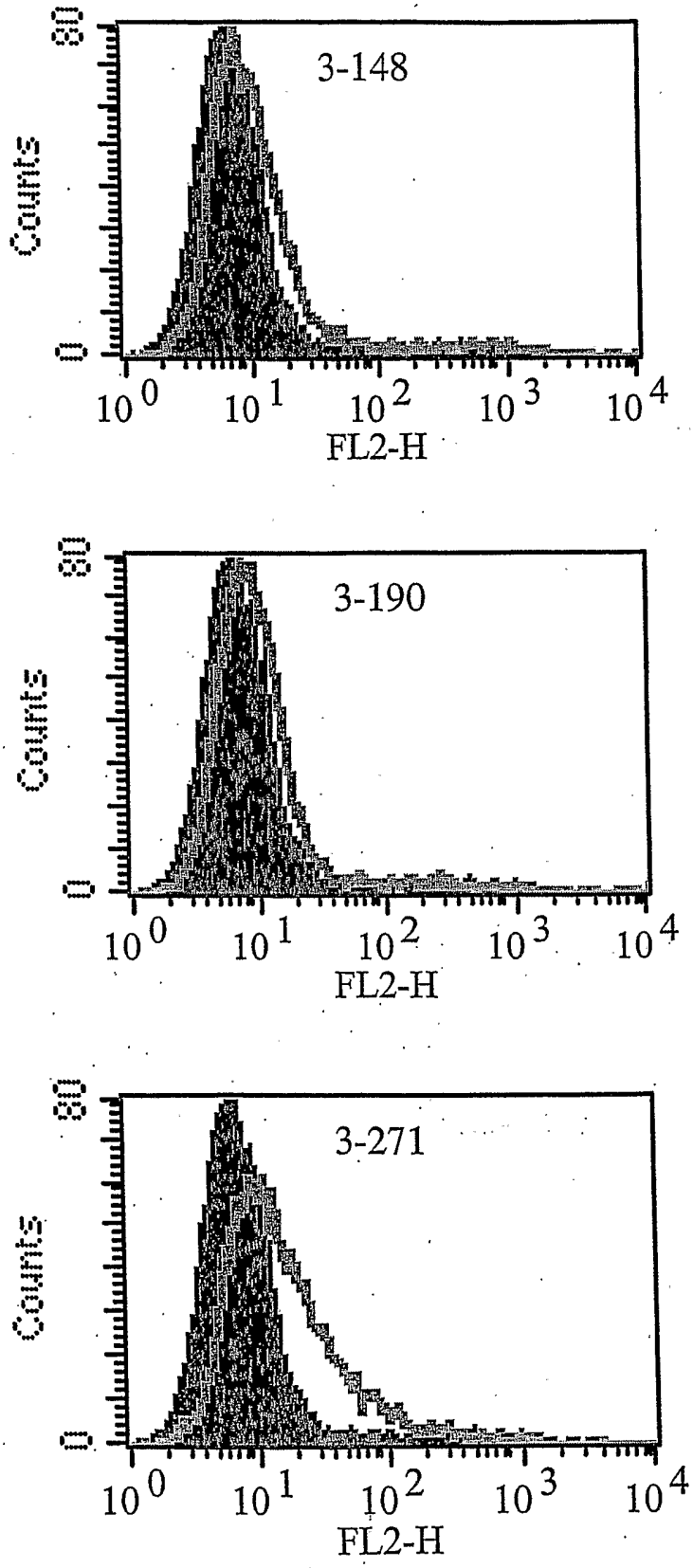


Fig. 18 (cont.) KatoIII

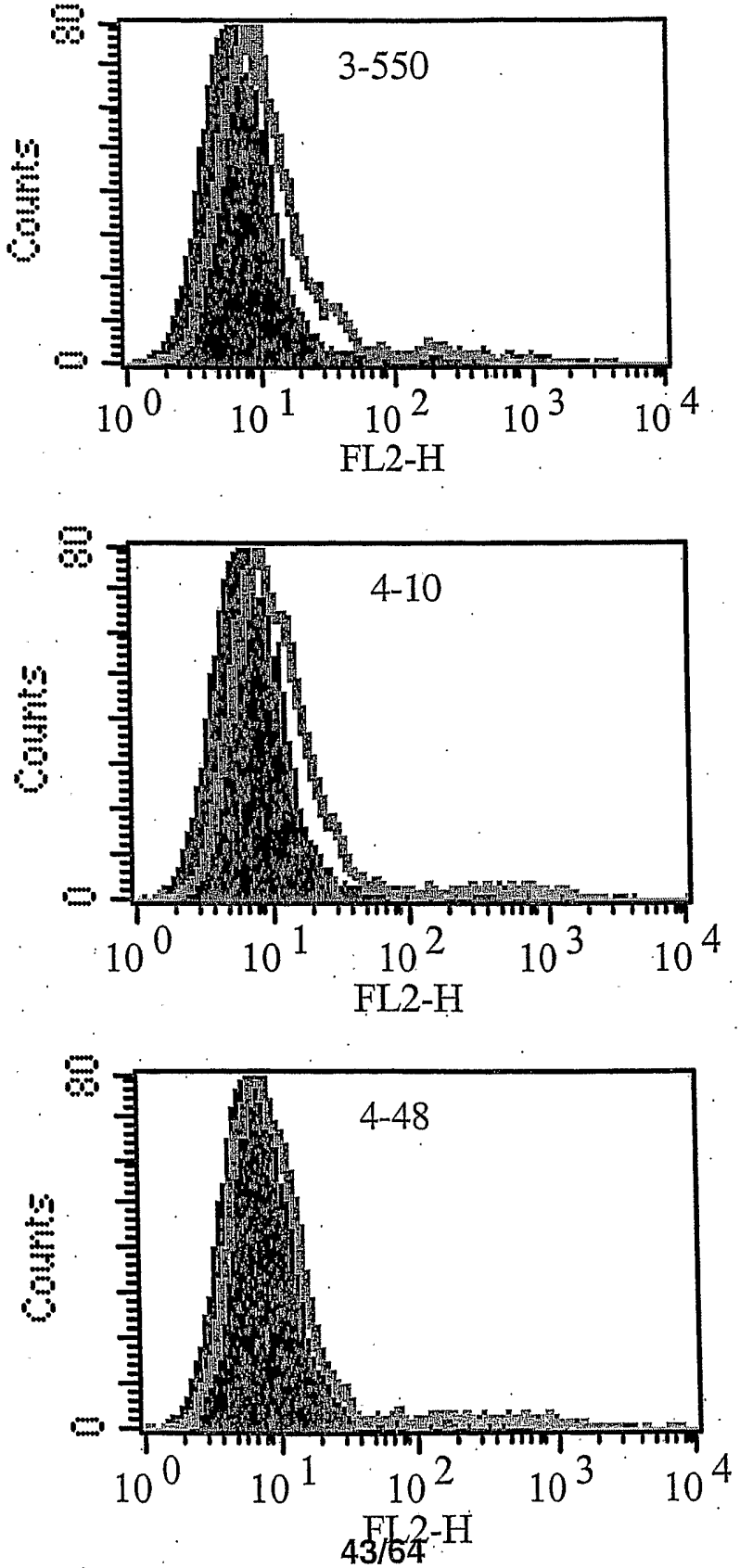


Fig. 18(cont.) KatoIII

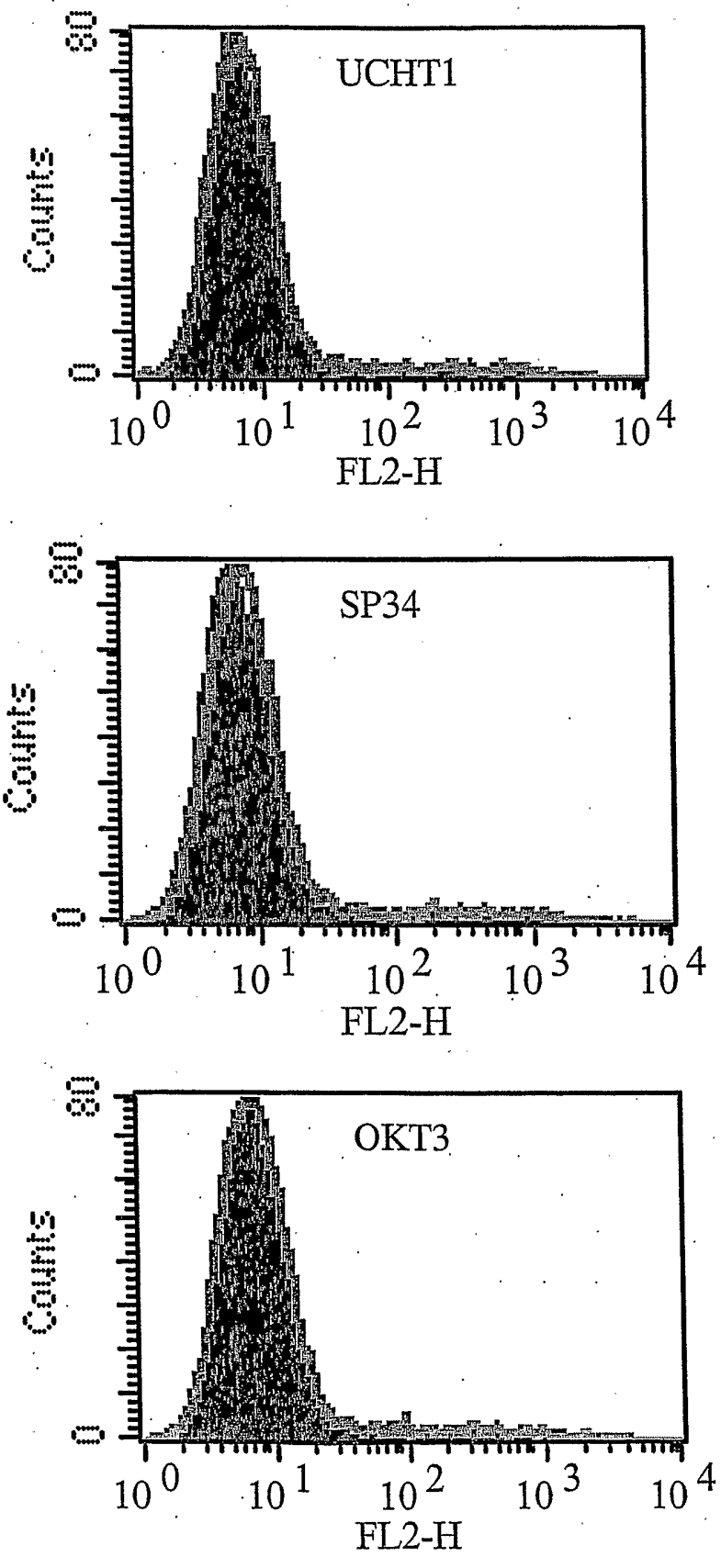
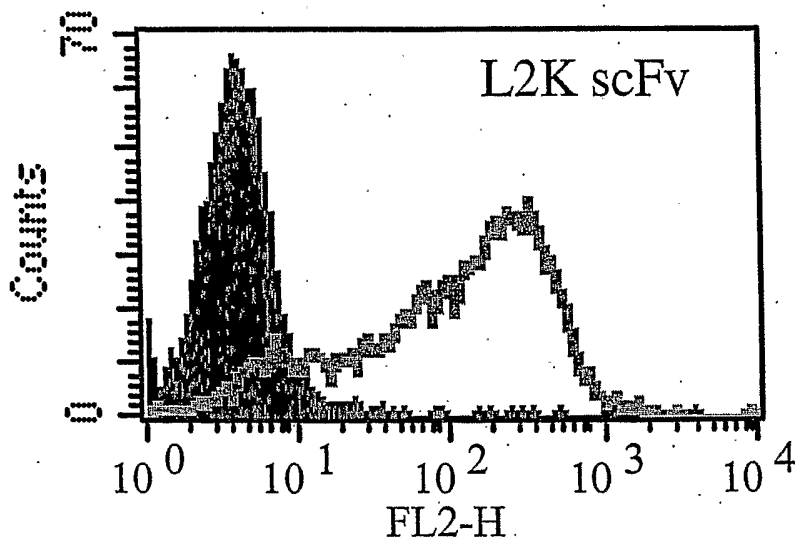


Fig. 19 Jurkat



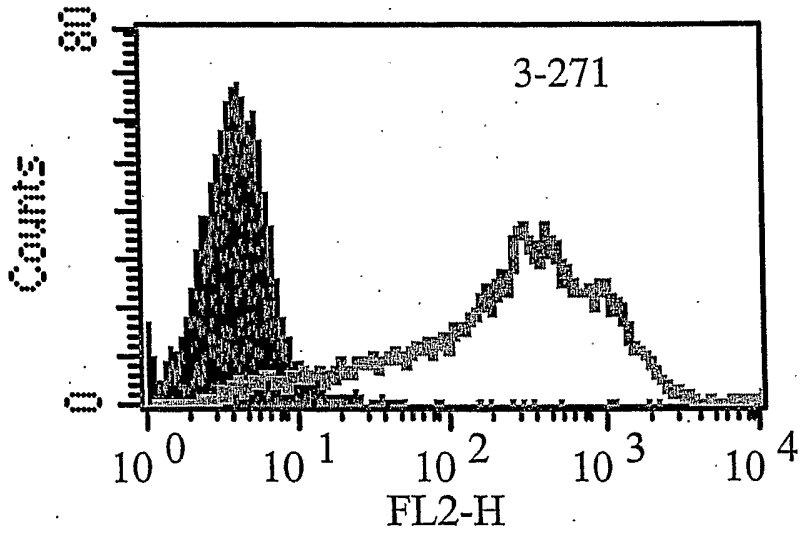


Fig. 19 (cont.) Jurkat

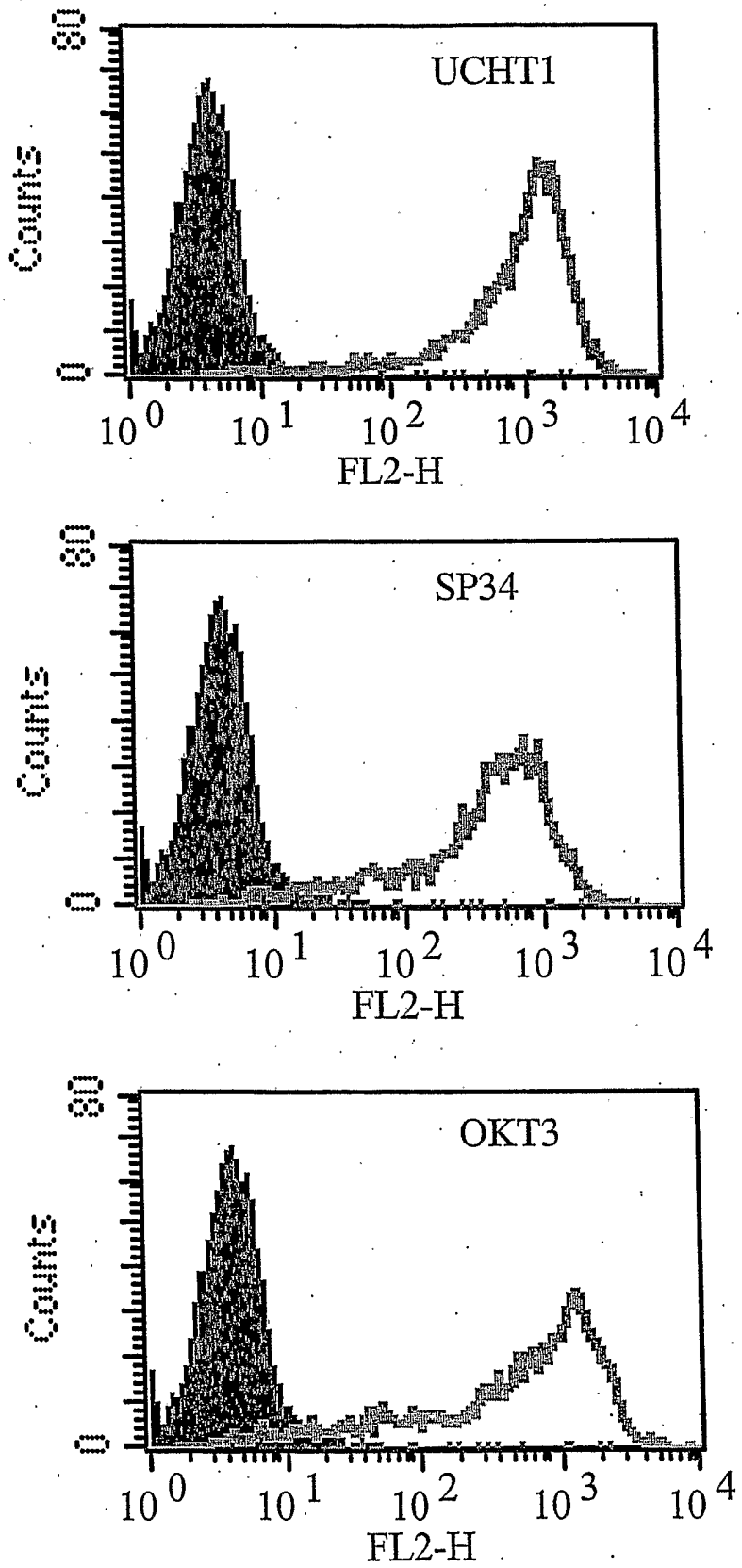
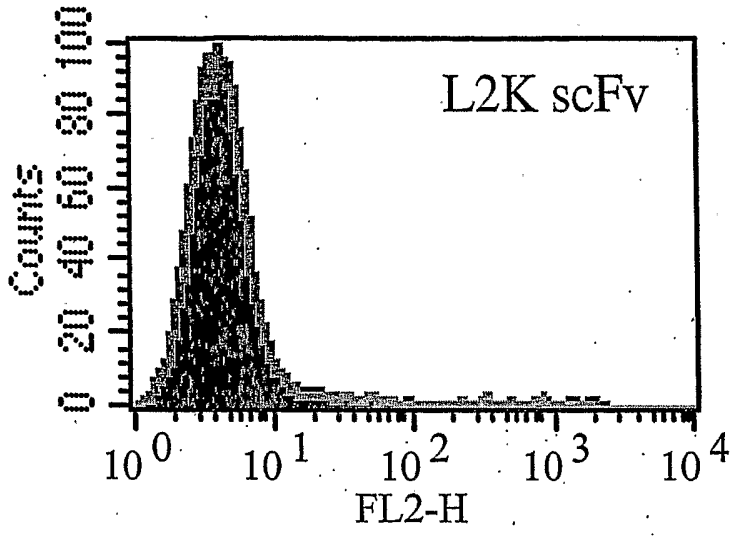


Fig. 20

CHO


L2K scFv
Counts
0 20 40 60 80 100
10 0 10 1 10 2 10 3 10 4
FL2-H

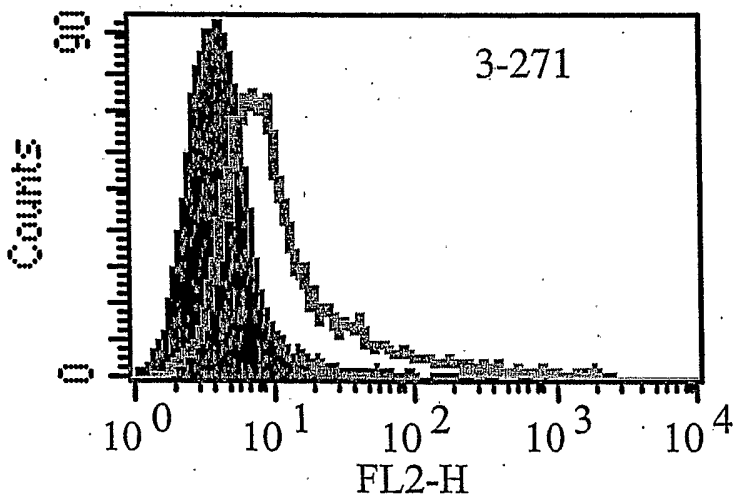

3-271
Counts
0 90
10 0 10 1 10 2 10 3 10 4
FL2-H

Fig. 20 (cont.) CHO

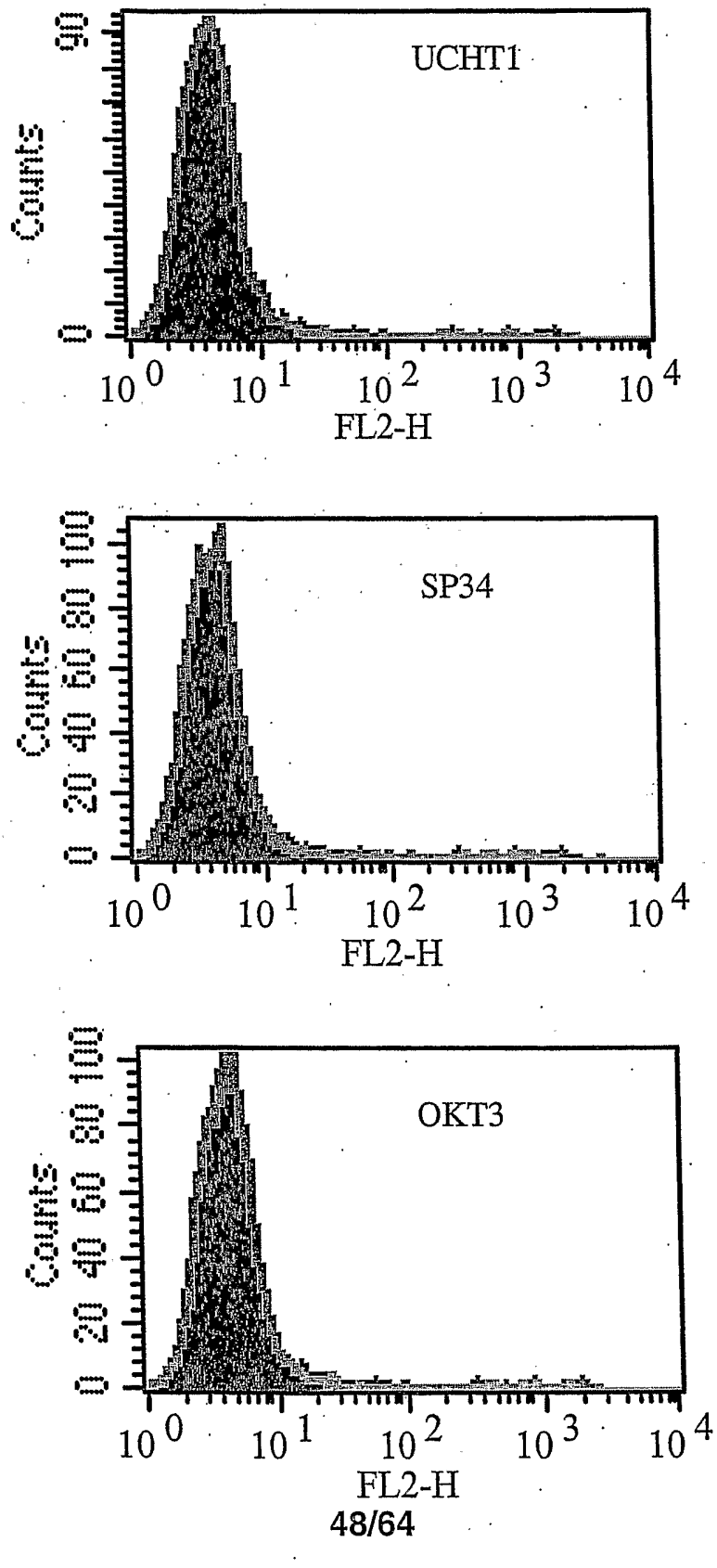
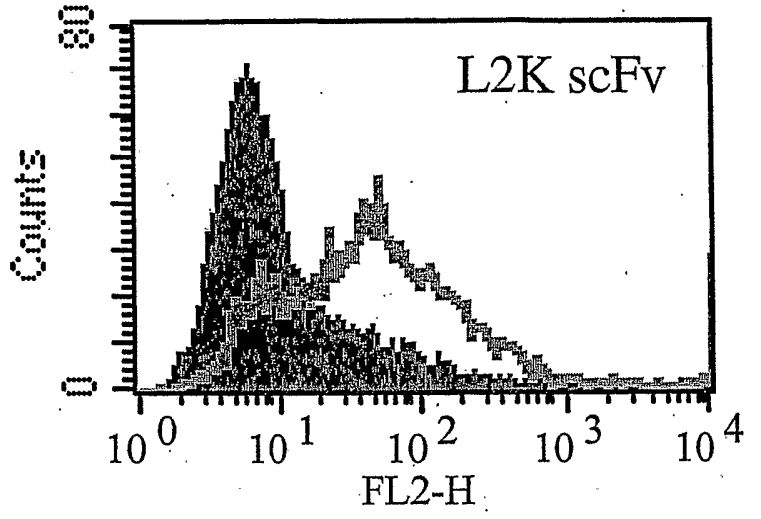


Fig. 21 CHO/CD3e-g



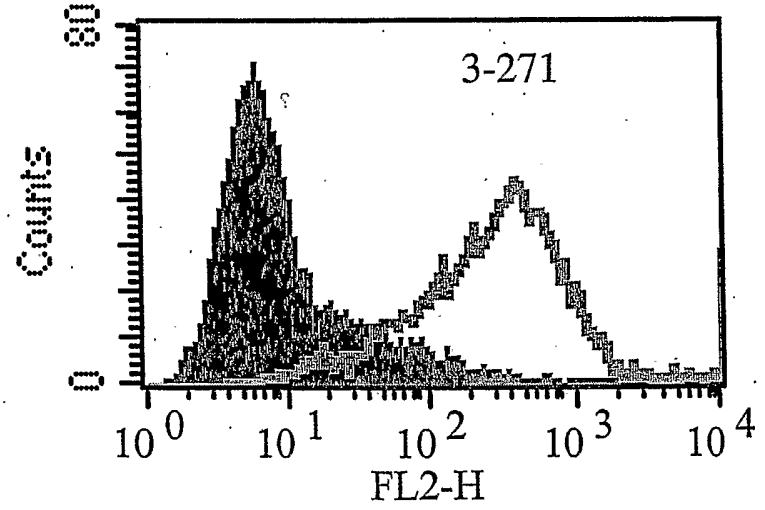
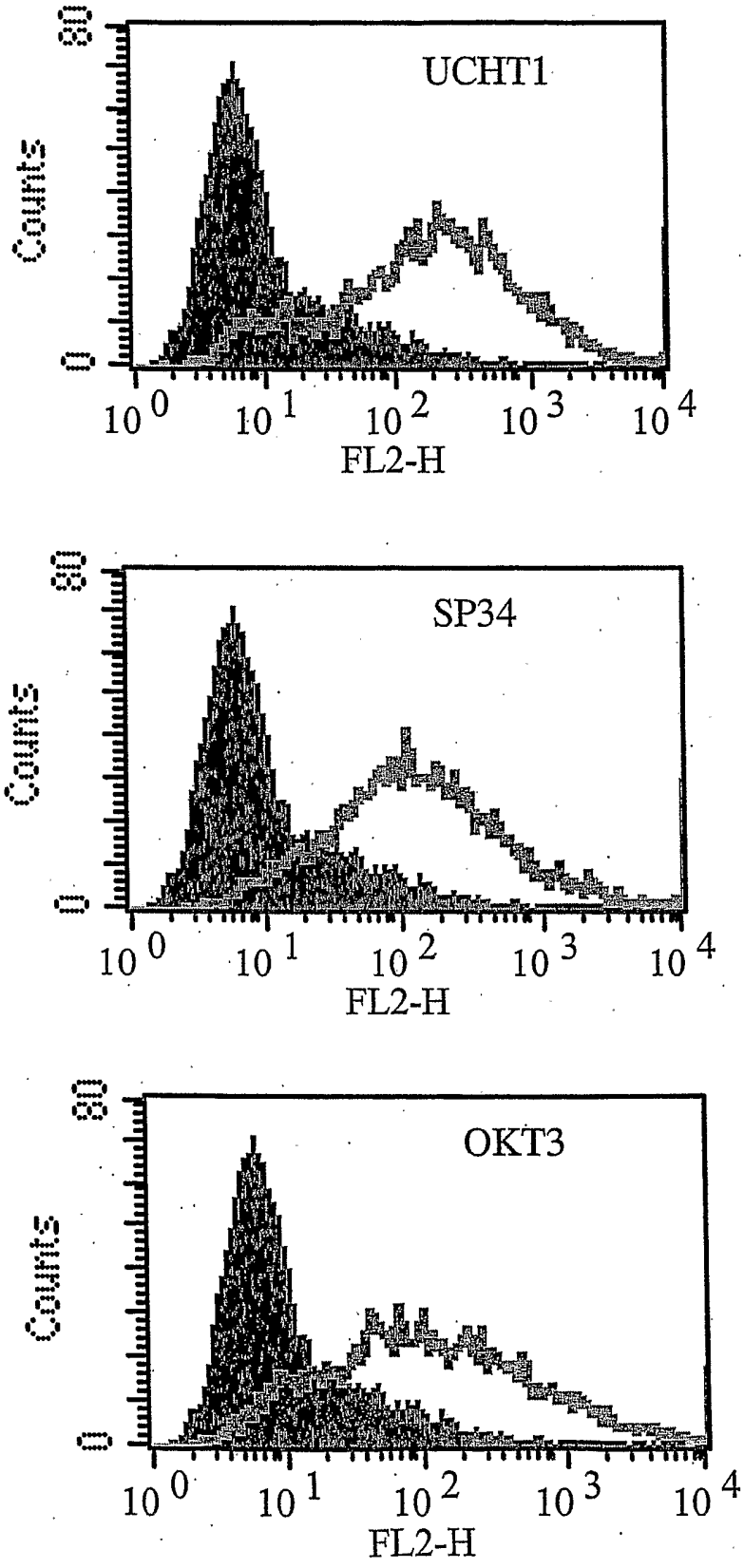


Fig. 21 (cont.) CHO/CD3e-g



EpCAM 5-10

```
                E  V  Q  L  L  E  Q        S  G  A        E  L  V  R  P  G  T        S  V  K
1   GAGGTGCAGC TGCTCGAGCA GTCTGGAGCT GAGCTGGTAA GGCCTGGGAC TTCAGTGAAG
    CTCCACGTCG ACGAGCTCGT CAGACCTCGA CTCGACCATT CCGGACCCTG AAGTCACTTC

                I  S  C  K  A  S  G        Y  A  F        T  N  Y  W  L  G  W        V  K  Q
61  ATATCCTGCA AGGCTTCTGG ATACGCCTTC ACTAACTACT GGCTAGGTTG GGTAAAGCAG
    TATAGGACGT TCCGAAGACC TATGCGGAAG TGATTGATGA CCGATCCAAC CCATTTCGTC

                R  P  G  H  G  L  E        W  I  G        D  I  F  P  G  S  G        N  I  H
121 AGGCCTGGAC ATGGACTTGA GTGGATTGGA GATATTTTCC CTGGAAGTGG TAATATCCAC
    TCCGGACCTG TACCTGAACT CACCTAACCT CTATAAAAGG GACCTTCACC ATTATAGGTG

                Y  N  E  K  F  K  G        K  A  T        L  T  A  D  K  S  S        S  T  A
181 TACAATGAGA AGTTCAAGGG CAAAGCCACA CTGACTGCAG ACAAATCTTC GAGCACAGCC
    ATGTTACTCT TCAAGTTCCC GTTTCGGTGT GACTGACGTC TGTTTAGAAG CTCGTGTCGG
```

Fig. 22

```
                Y  M  Q  L  S  S  S  L  T  F  E  D  S  A  V  Y  Y  F  C  A  R  L
241  TATATGCAGC TCAGTAGCCT GACATTTGAG GACTCTGCTG TCTATTTCTG TGCAAGACTG
     ATATACGTCG AGTCATCGGA CTGTAAACTC CTGAGACGAC AGATAAAGAC ACGTTCTGAC

                R  N  W  D  E  P  M  D  Y  W  G  Q  G  T  T  V  T  V  S  S
301  AGGAACTGGG ACGAGCCTAT GGACTACTGG GGCCAAGGGA CCACGGTCAC CGTCTCCTCA
     TCCTTGACCC TGCTCGGATA CCTGATGACC CCGGTTCCCT GGTGCCAGTG GCAGAGGAGT

                G  G  G  G  S  G  G  G  S  G  G  G  G  S  E  L  V  M  T
361  GGTGGTGGTG GTTCTGGCGG CGGCGGCTCC GGTGGTGGTG GTTCTGAGCT CGTGATGACA
     CCACCACCAC CAAGACCGCC GCCGCCGAGG CCACCACCAC CAAGACTCGA GCACTACTGT

                Q  S  P  S  S  L  T  V  T  A  G  E  K  V  T  M  S  C  K  S
421  CAGTCTCCAT CCTCCCTGAC TGTGACAGCA GGAGAGAAGG TCACTATGAG CTGCAAGTCC
     GTCAGAGGTA GGAGGGACTG ACACTGTCGT CCTCTCTTCC AGTGATACTC GACGTTCAGG

                S  Q  S  L  L  N  S  G  N  Q  K  N  Y  L  T  W  Y  Q  Q  K
481  AGTCAGAGTC TGTTAAACAG TGGAAATCAA AAGAACTACT TGACCTGGTA CCAGCAGAAA
     TCAGTCTCAG ACAATTTGTC ACCTTTAGTT TTCTTGATGA ACTGGACCAT GGTCGTCTTT
```

Fig. 22 (cont.)

```
                P  G  Q  P  P  K  L  L  I  Y  W  A  S  T  R  E  S  G  V  P
            CCAGGGCAGC CTCCTAAACT GTTGATCTAC TGGGCATCCA CTAGGGAATC TGGGGTCCCT
541         GGTCCCGTCG GAGGATTTGA CAACTAGATG ACCCGTAGGT GATCCCTTAG ACCCCAGGGA

                D  R  F  T  G  S  G  S  G  T  D  F  T  L  T  I  S  S  V  Q
            GATCGCTTCA CAGGCAGTGG ATCTGGAACA GATTTCACTC TCACCATCAG CAGTGTGCAG
601         CTAGCGAAGT GTCCGTCACC TAGACCTTGT CTAAAGTGAG AGTGGTAGTC GTCACACGTC

                A  E  D  L  A  V  Y  Y  C  Q  N  D  Y  S  Y  P  L  T  F  G
            GCTGAAGACC TGGCAGTTTA TTACTGTCAG AATGATTATA GTTATCCGCT CACGTTCGGT
661         CGACTTCTGG ACCGTCAAAT AATGACAGTC TTACTAATAT CAATAGGCGA GTGCAAGCCA

                A  G  T  K  L  E  I  K
            GCTGGGACCA AGCTTGAGAT CAAA
721         CGACCCTGGT TCGAACTCTA GTTT
```

Fig. 22 (cont.)

CD19

```
      Q  V  Q  L     Q  Q  S     G  A  E     L  V  R  P     G  S  S     V  K  I
1     CAGGTGCAGC TGCAGCAGTC TGGGGCTGAG CTGGTGAGGC CTGGGTCCTC AGTGAAGATT
      GTCCACGTCG ACGTCGTCAG ACCCCGACTC GACCACTCCG GACCCAGGAG TCACTTCTAA

      S  C  K  A     S  G  Y     A  F  S     S  Y  W  M     N  W  V     K  Q  R
61    TCCTGCAAGG CTTCTGGCTA TGCATTCAGT AGCTACTGGA TGAACTGGGT GAAGCAGAGG
      AGGACGTTCC GAAGACCGAT ACGTAAGTCA TCGATGACCT ACTTGACCCA CTTCGTCTCC

      P  G  Q  G     L  E  W     I  G  Q     I  W  P  G     D  G  D     T  N  Y
121   CCTGGACAGG GTCTTGAGTG GATTGGACAG ATTTGGCCTG GAGATGGTGA TACTAACTAC
      GGACCTGTCC CAGAACTCAC CTAACCTGTC TAAACCGGAC CTCTACCACT ATGATTGATG

      N  G  K  F     K  G  K     A  T  L     T  A  D  E     S  S  S     T  A  Y
181   AATGGAAAGT TCAAGGGTAA AGCCACTCTG ACTGCAGACG AATCCTCCAG CACAGCCTAC
      TTACCTTTCA AGTTCCCATT TCGGTGAGAC TGACGTCTGC TTAGGAGGTC GTGTCGGATG
```

Fig. 23

```
          M  Q  L  S   S  L  A   S  E  D   S  A  V  Y   F  C  A   R  R  E
241  ATGCAACTCA GCAGCCTAGC ATCTGAGGAC TCTGCGGTCT ATTTCTGTGC AAGACGGGAG
     TACGTTGAGT CGTCGGATCG TAGACTCCTG AGACGCCAGA TAAAGACACG TTCTGCCCTC

          T  T  T  V   G  R  Y   Y  Y  A   M  D  Y  W   G  Q  G   T  T  V
301  ACTACGACGG TAGGCCGTTA TTACTATGCT ATGGACTACT GGGGCCAAGG GACCACGGTC
     TGATGCTGCC ATCCGGCAAT AATGATACGA TACCTGATGA CCCCGGTTCC CTGGTGCCAG

          T  V  S  S   G  G  G   G  S  G   G  G  G  S   G  G  G   G  S  D
361  ACCGTCTCCT CCGGTGGTGG TGGTTCTGGC GGCGGCGGCT CCGGTGGTGG TGGTTCTGAT
     TGGCAGAGGA GGCCACCACC ACCAAGACCG CCGCCGCCGA GGCCACCACC ACCAAGACTA

          I  Q  L  T   Q  S  P   A  S  L   A  V  S  L   G  Q  R   A  T  I
421  ATCCAGCTGA CCCAGTCTCC AGCTTCTTTG GCTGTGTCTC TAGGGCAGAG GGCCACCATC
     TAGGTCGACT GGGTCAGAGG TCGAAGAAAC CGACACAGAG ATCCCGTCTC CCGGTGGTAG

          S  C  K  A   S  Q  S   V  D  Y   D  G  D  S   Y  L  N   W  Y  Q
481  TCCTGCAAGG CCAGCCAAAG TGTTGATTAT GATGGTGATA GTTATTTGAA CTGGTACCAA
     AGGACGTTCC GGTCGGTTTC ACAACTAATA CTACCACTAT CAATAAACTT GACCATGGTT
```

Fig. 23 (cont.)

```
          Q  I  P  G  Q  P  P     K  L  L     I  Y  D  A     S  N  L     V  S  G
541  CAGATTCCAG GACAGCCACC CAAACTCCTC ATCTATGATG CATCCAATCT AGTTTCTGGG
     GTCTAAGGTC CTGTCGGTGG GTTTGAGGAG TAGATACTAC GTAGGTTAGA TCAAAGACCC

          I  P  P  R     F  S  G     S  G  S     G  T  D  F     T  L  N     I  H  P
601  ATCCCACCCA GGTTTAGTGG CAGTGGGTCT GGGACAGACT TCACCCTCAA CATCCATCCT
     TAGGGTGGGT CCAAATCACC GTCACCCAGA CCCTGTCTGA AGTGGGAGTT GTAGGTAGGA

          V  E  K  V     D  A  A     T  Y  H     C  Q  Q  S     T  E  D     P  W  T
661  GTGGAGAAGG TGGATGCTGC AACCTATCAC TGTCAGCAAA GTACTGAGGA TCCGTGGACG
     CACCTCTTCC ACCTACGACG TTGGATAGTG ACAGTCGTTT CATGACTCCT AGGCACCTGC

          F  G  G  G     T  K  L     E  I  K
721  TTCGGTGGAG GGACCAAGCT CGAGATCAAA
     AAGCCACCTC CCTGGTTCGA GCTCTAGTTT
```

Fig. 23 (cont.)

```
                Q  V  Q  L  R  Q  P     G  A  E  L  V  K  P  G  A  S     V  K  M
1   CAGGTGCAAC TGCGGCAGCC TGGGGCTGAG CTGGTGAAGC CTGGGGCCTC AGTGAAGATG
    GTCCACGTTG ACGCCGTCGG ACCCCGACTC GACCACTTCG GACCCCGGAG TCACTTCTAC

                S  C  K  A  S  G  Y     T  F  T  S  Y  N  M  H  W  V     K  Q  T
61  TCCTGCAAGG CTTCTGGCTA CACATTTACC AGTTACAATA TGCACTGGGT AAAGCAGACA
    AGGACGTTCC GAAGACCGAT GTGTAAATGG TCAATGTTAT ACGTGACCCA TTTCGTCTGT

                P  G  Q  G  L  E  W     I  G  A  I  Y  P  G  N  G  D     T  S  Y
121 CCTGGACAGG GCCTGGAATG GATTGGAGCT ATTTATCCAG GAAATGGTGA TACTTCCTAC
    GGACCTGTCC CGGACCTTAC CTAACCTCGA TAAATAGGTC CTTTACCACT ATGAAGGATG

                N  Q  K  F  K  G  K     A  T  L  T  A  D  K  S  S  S     T  A  Y
181 AATCAGAAGT TCAAAGGCAA GGCCACATTG ACTGCAGACA AATCCTCCAG CACAGCCTAC
    TTAGTCTTCA AGTTTCCGTT CCGGTGTAAC TGACGTCTGT TTAGGAGGTC GTGTCGGATG
```

Fig. 24

```
        M  Q  L  S   S  L  T   S  E  D   S  A  V  Y   Y  C  A   R  S  H
241  ATGCAGCTCA GCAGTCTGAC ATCTGAGGAC TCTGCGGTCT ATTACTGTGC AAGATCGCAC
     TACGTCGAGT CGTCAGACTG TAGACTCCTG AGACGCCAGA TAATGACACG TTCTAGCGTG

      Y  G  S  N   Y  V  D   Y  F  D   Y  W  G  Q   G  T  L   V  T  V
301  TACGGTAGTA ACTACGTAGA CTACTTTGAC TACTGGGGCC AAGGCACACT AGTCACAGTC
     ATGCCATCAT TGATGCATCT GATGAAACTG ATGACCCCGG TTCCGTGTGA TCAGTGTCAG

      S  T  G  G   G  G  S   G  G  G   G  S  G  G   G  G  S   Q  I  V
361  TCGACAGGTG GTGGTGGTTC TGGCGGCGGC GGCTCCGGTG GTGGTGGTTC TCAAATTGTT
     AGCTGTCCAC CACCACCAAG ACCGCCGCCG CCGAGGCCAC CACCACCAAG AGTTTAACAA

      L  S  Q  S   P  A  I   L  S  A   S  P  G  E   K  V  T   M  T  C
421  CTCTCCCAGT CTCCAGCAAT CCTTTCTGCA TCTCCAGGGG AGAAGGTCAC AATGACTTGC
     GAGAGGGTCA GAGGTCGTTA GGAAAGACGT AGAGGTCCCC TCTTCCAGTG TTACTGAACG
```

Fig. 24 (cont.)

```
                R  A  S  S  S  L  S     F  M  H     W  Y  Q  Q  K  P  G     S  S  P
481  AGGGCCAGCT CAAGTTTAAG TTTCATGCAC TGGTACCAGC AGAAGCCAGG ATCCTCCCCC
     TCCCGGTCGA GTTCAAATTC AAAGTACGTG ACCATGGTCG TCTTCGGTCC TAGGAGGGGG

                K  P  W  I  Y  A  T     S  N  L     A  S  G  V  P  A  R     F  S  G
541  AAACCCTGGA TTTATGCCAC ATCCAACCTG GCTTCTGGAG TCCCTGCTCG CTTCAGTGGC
     TTTGGGACCT AAATACGGTG TAGGTTGGAC CGAAGACCTC AGGGACGAGC GAAGTCACCG

                S  G  S  G  T  S  Y     S  L  T     I  S  R  V  E  A  E     D  A  A
601  AGTGGGTCTG GGACCTCTTA CTCTCTCACA ATCAGCAGAG TGGAGGCTGA AGATGCTGCC
     TCACCCAGAC CCTGGAGAAT GAGAGAGTGT TAGTCGTCTC ACCTCCGACT TCTACGACGG

                T  Y  F  C  H  Q  W     S  S  N     P  L  T  F  G  A  G     T  K  V
661  ACTTATTTCT GCCATCAGTG GAGTAGTAAC CCGCTCACGT TCGGTGCTGG GACAAAGGTG
     TGAATAAAGA CGGTAGTCAC CTCATCATTG GGCGAGTGCA AGCCACGACC CTGTTTCCAC

                E  I  K
721  GAAATAAAA
     CTTTATTTT
```

Fig. 24 (cont.)

```
                Q  L  E  Q  S  G  G  P  E  L  K  K  P  G  G  E  T  V  T  I  S  C
1               CAGCTGGAGC AGTCTGGACC TGAACTGAAG AAGCCTGGAG AGACAGTCAC GATCTCCTGC
                GTCGACCTCG TCAGACCTGG ACTTGACTTC TTCGGACCTC TCTGTCAGTG CTAGAGGACG

                K  A  S  G  Y  T  F  T  K  F  G  M  N  W  V  K  Q  A  P  G
61              AAGGCTTCTG GGTATACCTT CACGAAGTTC GGAATGAACT GGGTGAAGCA GGCTCCAGGA
                TTCCGAAGAC CCATATGGAA GTGCTTCAAG CCTTACTTGA CCCACTTCGT CCGAGGTCCT

                K  G  L  K  W  M  G  W  I  H  T  S  T  G  E  P  T  Y  S  D
121             AAGGGTTTAA AGTGGATGGG CTGGATACAC ACCTCCACTG GAGAGCCAAC ATATTCTGAT
                TTCCCAAATT TCACCTACCC GACCTATGTG TGGAGGTGAC CTCTCGGTTG TATAAGACTA

                D  F  K  G  R  F  A  F  S  L  E  T  S  A  S  T  A  Y  L  R
181             GACTTCAAGG GACGGTTTGC CTTCTCTTTG GAAACGTCTG CCAGCACTGC CTATTTGCGG
                CTGAAGTTCC CTGCCAAACG GAAGAGAAAC CTTTGCAGAC GGTCGTGACG GATAAACGCC
```

Fig. 25

```
                I  N  N  L  K  N  E     D  M  A     K  Y  F  C  A  R  G     G  P  Y
241   ATCAACAACC TCAAAAATGA GGACATGGCT AAATACTTCT GTGCCAGAGG TGGTCCTTAC
      TAGTTGTTGG AGTTTTTACT CCTGTACCGA TTTATGAAGA CACGGTCTCC ACCAGGAATG

                V  R  G  A  L  D  Y     W  G  Q     G  T  S  V  T  V  S     S  G  G
301   GTAAGGGGTG CTTTGGACTA CTGGGGTCAA GGAACCTCAG TCACCGTCTC CTCCGGTGGT
      CATTCCCCAC GAACCTGAT  GACCCCAGTT CCTTGGAGTC AGTGGCAGAG GAGGCCACCA

                G  G  S  G  G  G  G     S  G  G     G  G  S  D  I  I  L     I  Q  S
361   GGTGGTTCTG GCGGCGGCGG CTCCGGTGGT GGTGGTTCTG ACATTATCCT GATCCAATCT
      CCACCAAGAC CGCCGCCGCC GAGGCCACCA CCACCAAGAC TGTAATAGGA CTAGGTTAGA

                P  P  S  L  A  V  S     L  G  Q     R  A  T  I  S  C  R     T  S  E
421   CCACCTTCTT TGGCTGTGTC TCTAGGGCAG AGGGCCACCA TCTCCTGCAG AACCAGCGAA
      GGTGGAAGAA ACCGACACAG AGATCCCGTC TCCCGGTGGT AGAGGACGTC TTGGTCGCTT
```

Fig. 25 (cont.)

```
                N  V  D  G  Y  G  G  I     S  F  I     N  W  Y  Q  Q  K  P     G  Q  P
481             AATGTTGACG GATACGGCAT TAGTTTTATA AACTGGTACC AACAGAAGCC AGGACAGCCA
                TTACAACTGC CTATGCCGTA ATCAAAATAT TTGACCATGG TTGTCTTCGG TCCTGTCGGT

                P  K  L  L  I  Y  A     A  S  H     Q  G  S  G  V  P  A     R  F  S
541             CCCAAACTCC TCATCTATGC TGCATCCCAC CAAGGATCCG GGGTCCCTGC CAGATTTAGT
                GGGTTTGAGG AGTAGATACG ACGTAGGGTG GTTCCTAGGC CCCAGGGACG GTCTAAATCA

                G  S  G  S  G  T  D     F  S  L     N  I  H  P  L  E  E     D  D  T
601             GGCAGTGGGT CTGGGACAGA CTTCAGCCTC AACATCCATC CTTTGGAGGA GGATGATACT
                CCGTCACCCA GACCCTGTCT GAAGTCGGAG TTGTAGGTAG GAAACCTCCT CCTACTATGA

                A  M  Y  F  C  H  Q     S  K  K     V  P  W  T  F  G  G     G  T  K
661             GCAATGTATT TCTGTCACCA AAGTAAGAAG GTTCCGTGGA CGTTCGGTGG AGGCACCAAG
                CGTTACATAA AGACAGTGGT TTCATTCTTC CAAGGCACCT GCAAGCCACC TCCGTGGTTC

                L  E  I  K
721             CTGGAAATCA AA
                GACCTTTAGT TT
```

Fig. 25 (cont.)

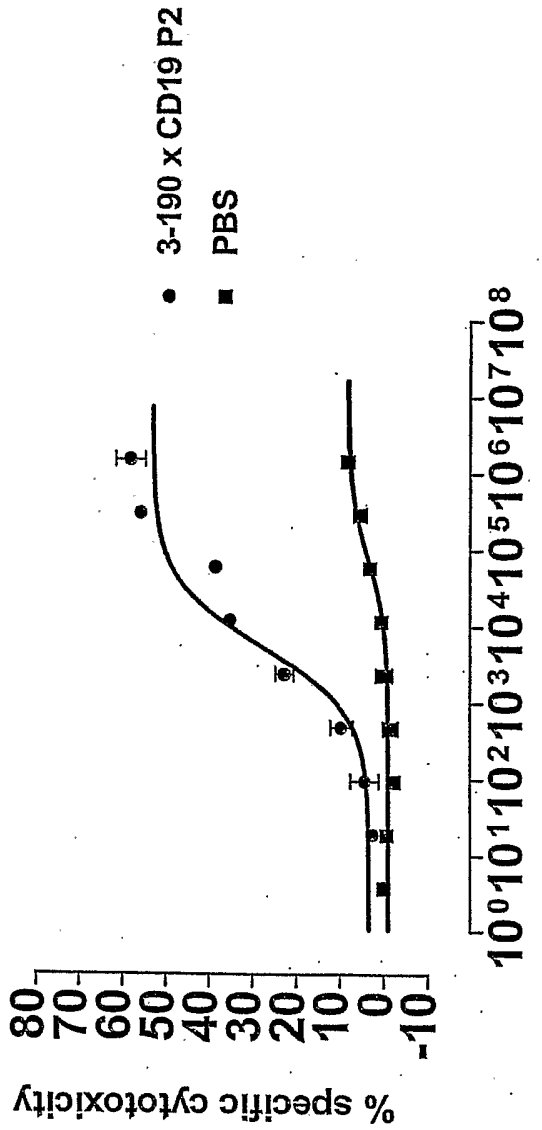

3-190 x CD19 P2
PBS
% specific cytotoxicity
80
70
60
50
40
30
20
10
0
-10
10^0 10^1 10^2 10^3 10^4 10^5 10^6 10^7 10^8
concentration [pg/ml]

Fig. 26

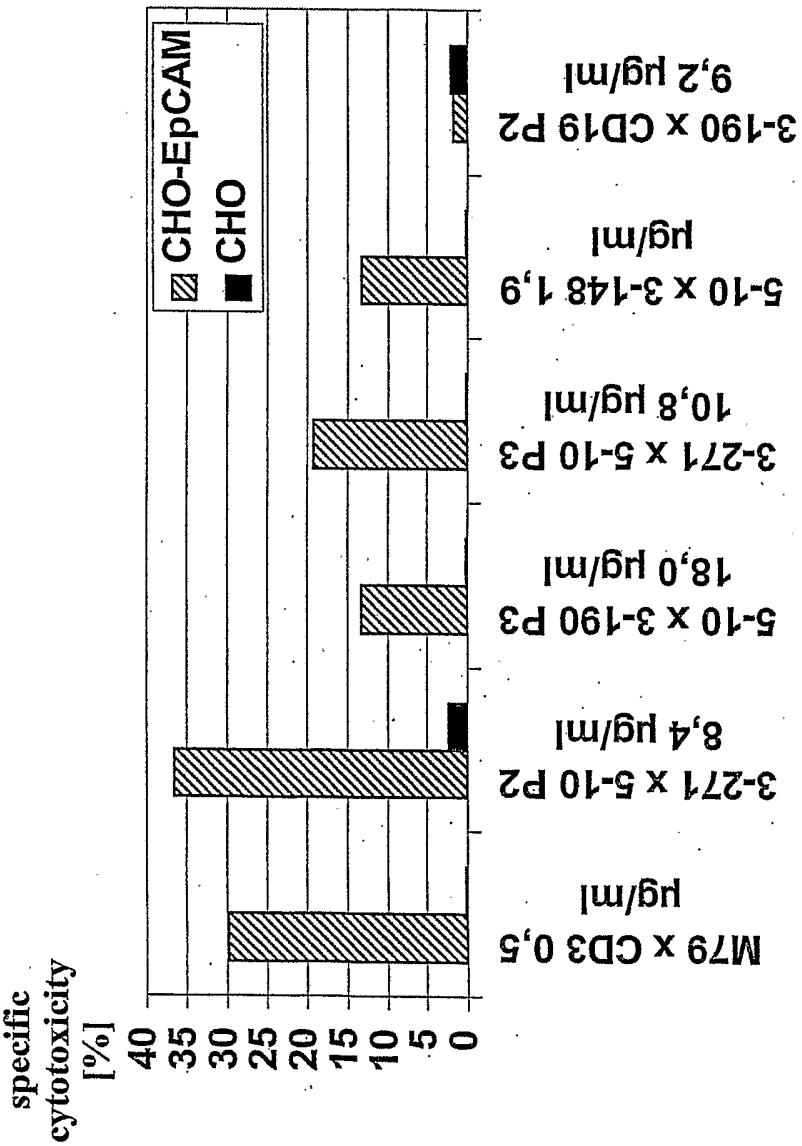

specific cytotoxicity [%]
40
35
30
25
20
15
10
5
0
CHO-EpCAM
CHO
M79 x CD3 0,5 µg/ml
3-271 x 5-10 P2 8,4 µg/ml
5-10 x 3-190 P3 18,0 µg/ml
3-271 x 5-10 P3 10,8 µg/ml
5-10 x 3-148 1,9 µg/ml
3-190 x CD19 P2 9,2 µg/ml

Fig. 27

SEQUENCE LISTING

<110> Micromet AG

<120> Human anti-human CD3 Binders

<130> H1524 PCT

<150> EP 03012132.1

<151> 2003-05-31

<160> 252

<170> PatentIn version 3.1

<210> 1

<211> 375

<212> DNA

<213> artificial sequence

<220>

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ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtaa taaatactac 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag atctgaggac acggccgtgt attactgtgc gaggctcagc 300

ccgtattgta ctaatggtgt atgctgggat gcttttgata tctggggcca agggacaatg 360

gtcaccgtct cctca 375

<210> 2

<211> 125

<212> PRT

<213> artificial sequence

<220>

<223> 3-106 VH: aa

<400> 2

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

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn 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 Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Ser Pro Tyr Cys Thr Asn Gly Val Cys Trp Asp Ala Phe
100 105 110

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

<210> 3

<211> 15

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<213> artificial sequence

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<400> 3
agctatggca tgcac 15

<210> 4

<211> 5

<212> PRT

<213> artificial sequence

<220>

<223> 3-106 VH: CDR1 aa

<400> 4

Ser Tyr Gly Met His
1 5

<210> 5

<211> 51

<212> DNA

<213> artificial sequence

<220>

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<210> 6

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> 3-106 VH: CDR2 aa

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

Gly

<210> 7

<211> 48

<212> DNA

<213> artificial sequence

<220>

<223> 3-106 VH: CDR3 nuc

<400> 7
ctcagcccgt attgtactaa tggtgtatgc tgggatgctt ttgatatc 48

<210> 8

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> 3-106 VH: CDR3 aa

<400> 8

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

<210> 9

<211> 321

<212> DNA

<213> artificial sequence

<220>

<223> 3-106 VL: nuc

<400> 9

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atcacttgtc gggcaagtca gaccattagc aattatttaa attggtatca actgaagcca 120

gggaaagccc ctaagctcct gatctatgct gcatccactt tgcaaagtga ggtcccaacc 180

aggttcagtg gcagtgggtc tgggacagat ttcactctca ccatcagtgg tctgcatcct 240

gaagattttg caacttacta ctgtcaacag tttaatagtt atcctcgaac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> 10

<211> 107

<212> PRT

<213> artificial sequence

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

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

Tyr Ala Ala Ser Thr Leu Gln Ser Glu Val Pro Thr Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu His Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Arg
85 90 95

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

<210> 11

<211> 33

<212> DNA

<213> artificial sequence

<220>

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<210> 12

<211> 11

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Arg Ala Ser Gln Thr Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 13

<211> 21

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<400> 13
gctgcatcca ctttgcaaag t 21

<210> 14

<211> 7

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<220>

<223> 3-106 VL: CDR2 aa

<400> 14

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 15

<211> 27

<212> DNA

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<220>

<223> 3-106 VL: CDR3 nuc

<400> 15
caacagttta atagttatcc tcgaacg 27

<210> 16

<211> 9

<212> PRT

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<220>

<223> 3-106 VL: CDR3 aa

<400> 16

Gln Gln Phe Asn Ser Tyr Pro Arg Thr
1 5

<210> 17

<211> 366

<212> DNA

<213> artificial sequence

<220>

<223> 3-114 VH: nuc

<400> 17

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tcctgtacag cttctggatt caccttttggt gattatgcta tgagctggtt ccgccaggct 120

ccagggaagg ggctggagtg ggtaggtttc attagaagca aagcttatgg tgggacaaca 180

gaatacgccg cgtctgtgaa aggcagattc accatctcaa gagatgattc caaaagcatc 240

gcctatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatta ctgtactcca 300

cagctatggt tactacaaga tgcttttgat atctggggcc aagggacaat ggtcaccgtc 360

tcctca 366

<210> 18

<211> 122

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<223> 3-114 VH: aa

<400> 18

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1 5 10 15

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

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

Gly Phe Ile Arg Ser Lys Ala Tyr Gly Gly Thr Thr Glu Tyr Ala Ala
50 55 60

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

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

Tyr Cys Thr Pro Gln Leu Trp Leu Leu Gln Asp Ala Phe Asp Ile Trp

100 105 110

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

<210> 19

<211> 15

<212> DNA

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<220>

<223> 3-114 VH: CDR1 nuc

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<210> 20

<211> 5

<212> PRT

<213> artificial sequence

<220>

<223> 3-114 VH: CDR1 aa

<400> 20

Asp Tyr Ala Met Ser
1 5

<210> 21

<211> 57

<212> DNA

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<223> 3-114 VH: CDR2 nuc

<400> 21
ttcattagaa gcaaagctta tggtgggaca acagaatacg ccgcgtctgt gaaaggc 57

<210> 22

<211> 19

<212> PRT

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<220>

<223> 3-114 VH: CDR2 aa

<400> 22

Phe Ile Arg Ser Lys Ala Tyr Gly Gly Thr Thr Glu Tyr Ala Ala Ser
1 5 10 15

Val Lys Gly

<210> 23

<211> 33

<212> DNA

<213> artificial sequence

<220>

<223> 3-114 VH: CDR3 nuc

<400> 23
cagctatggt tactacaaga tgcttttgat atc 33

<210> 24

<211> 11

<212> PRT

<213> artificial sequence

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<223> 3-114 VH: CDR3 aa

<400> 24

Gln Leu Trp Leu Leu Gln Asp Ala Phe Asp Ile
1 5 10

<210> 25

<211> 321

<212> DNA

<213> artificial sequence

<220>

<223> 3-114 VL: nuc

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atcacttgcc gggcgagtca gggcattagc aattatttag cctggtatca gcagaaacca 120

gggaaagttc ctaagctcct gatctatgct gcatccactt tgcaatcagg ggtcccatct 180

cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta cccctccgac gttcggccaa 300

gggaccaagc tggagatcaa a 321

<210> 26

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> 3-114 VL: aa

<400> 26

Glu Leu 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 Gly Ile Ser Asn Tyr
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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> 27

<211> 33

<212> DNA

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<223> 3-114 VL: CDR1 nuc

<400> 27
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<210> 28

<211> 11

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<223> 3-114 VL: CDR1 aa

<400> 28

Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala
1 5 10

<210> 29

<211> 21

<212> DNA

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<220>

<223> 3-114 VL: CDR2 nuc

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gctgcatcca ctttgcaatc a 21

<210> 30

<211> 7

<212> PRT

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<223> 3-114 VL: CDR2 aa

<400> 30

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 31

<211> 27

<212> DNA

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<220>

<223> 3-114 VL: CDR3 nuc

<400> 31
caacagagtt acagtacccc tccgacg 27

<210> 32

<211> 9

<212> PRT

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<223> 3-114 VL: CDR3 aa

<400> 32

Gln Gln Ser Tyr Ser Thr Pro Pro Thr
1 5

<210> 33

<211> 360

<212> DNA

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<223> 3-148 VH: nuc

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acctgcgctg tctctggtgg ctccatcagc agtagaaact ggtggagttg ggtccgccag 120

cccccaggga aggggctgga gtggattggt gatatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagtgggtat 300

accagctgtc gtgatgcttt tgatatctgg ggccaaggga caatggtcac cgtctcctca 360

<210> 34

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> 3-148 VH: aa

<400> 34

Glu Leu Gln Leu Val 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 Ser Ser Arg
20 25 30

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

Ile Gly Asp Ile Tyr His Ser 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 Gln 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 Ser Gly Tyr Thr Ser Cys Arg Asp Ala Phe Asp Ile Trp Gly Gln
100 105 110

Gly Thr Met Val Thr Val Ser Ser
115 120

<210> 35

<211> 18

<212> DNA

<213> artificial sequence

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<223> 3-148 VH: CDR1 nuc

<400> 35
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<210> 36

<211> 6

<212> PRT

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<223> 3-148 VH: CDR1 aa

<400> 36

Ser Arg Asn Trp Trp Ser
1 5

<210> 37

<211> 48

<212> DNA

<213> artificial sequence

<220>

<223> 3-148 VH: CDR2 nuc

<400> 37
gatatctatc atagtgggag caccaactac aacccgtccc tcaagagt 48

<210> 38

<211> 16

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<220>

<223> 3-148 VH: CDR2 aa

<400> 38

Asp Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 39

<211> 33

<212> DNA

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<223> 3-148 VH: CDR3 nuc

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<210> 40

<211> 11

<212> PRT

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<223> 3-148 VH: CDR3 aa

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Gly Tyr Thr Ser Cys Arg Asp Ala Phe Asp Ile
1 5 10

<210> 41

<211> 321

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<223> 3-148 VL: nuc

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atcacttgcc gggcgagtca gggcattggc aattatttag cctggtatca gcagaaacca 120

gggcagcctc ctaagatgct catttactgg gcatcaatcc gggaatccgg ggtccctgac 180

cgattcagtg gcagcgggtc tgggacagac ttcactctca ccatcagcag cctgcaggct 240

gaagatgtgg cagtttacta ctgtcagcaa tattatagta atcctcagac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> 42

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> 3-148 VL: aa

<400> 42

Glu Leu Val Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Gly Asn Tyr
20 25 30

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

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

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

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

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

<210> 43

<211> 33

<212> DNA

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<223> 3-148 VL: CDR1 nuc

<400> 43
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<210> 44

<211> 11

<212> PRT

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<223> 3-148 VL: CDR1 aa

<400> 44

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1 5 10

<210> 45

<211> 21

<212> DNA

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<223> 3-148 VL: CDR2 nuc

<400> 45
tgggcatcaa tccgggaatc c 21

<210> 46

<211> 7

<212> PRT

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<223> 3-148 VL: CDR2 aa

<400> 46

Trp Ala Ser Ile Arg Glu Ser
1 5

<210> 47

<211> 27

<212> DNA

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<223> 3-148 VL: CDR3 nuc

<400> 47
cagcaatatt atagtaatcc tcagacg 27

<210> 48

<211> 9

<212> PRT

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<223> 3-148 VL: CDR3 aa

<400> 48

Gln Gln Tyr Tyr Ser Asn Pro Gln Thr
1 5

<210> 49

<211> 378

<212> DNA

<213> artificial sequence

<220>

<223> 3-190 VH: nuc

<400> 49

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ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggccgaggc 300

cgatttttgg ggtggttatt aggggctcc aactggttcg acccctgggg ccagggaacc 360

ctggtcaccg tctcctca 378

<210> 50

<211> 126

<212> PRT

<213> artificial sequence

<220>

<223> 3-190 VH: aa

<400> 50

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

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

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

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

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

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

Arg Gly Arg Gly Arg Phe Leu Gly Trp Leu Leu Gly Gly Ser Asn Trp
100 105 110

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

<210> 51

<211> 15

<212> DNA

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<220>

<223> 3-190 VH: CDR1 nuc

<400> 51
ggttactact ggagc 15

<210> 52

<211> 5

<212> PRT

<213> artificial sequence

<220>

<223> 3-190 VH: CDR1 aa

<400> 52

Gly Tyr Tyr Trp Ser
1 5

<210> 53

<211> 48

<212> DNA

<213> artificial sequence

<220>

<223> 3-190 VH: CDR2 nuc

<400> 53
gaaatcaatc atagtggaag caccaactac aacccgtccc tcaagagt 48

<210> 54

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> 3-190 VH: CDR2 aa

<400> 54

Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 55

<211> 54

<212> DNA

<213> artificial sequence

<220>

<223> 3-190 VH: CDR3 nuc

<400> 55
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<210> 56

<211> 18

<212> PRT

<213> artificial sequence

<220>

<223> 3-190 VH: CDR3 aa

<400> 56

Gly Arg Gly Arg Phe Leu Gly Trp Leu Leu Gly Gly Ser Asn Trp Phe
1 5 10 15

Asp Pro

<210> 57

<211> 321

<212> DNA

<213> artificial sequence

<220>

<223> 3-190 VL: nuc

<400> 57
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atcacttgcc gggcgagtca gggcattagc aattatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta ccccgtacac ttttggccag 300

gggaccaaag tggatatcaa a 321

<210> 58

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> 3-190 VL: aa

<400> 58

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> 59

<211> 33

<212> DNA

<213> artificial sequence

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<223> 3-190 VL: CDR1 nuc

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<210> 60

<211> 11

<212> PRT

<213> artificial sequence

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<223> 3-190 VL: CDR1 aa

<400> 60

Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 61

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 3-190 VL: CDR2 nuc

<400> 61
gatgcatcca atttggaaac a 21

<210> 62

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 3-190 VL: CDR2 aa

<400> 62

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> 63

<211> 27

<212> DNA

<213> artificial sequence

<220>

<223> 3-190 VL: CDR3 nuc

<400> 63
caacagagtt acagtacccc gtacact 27

<210> 64

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> 3-190 VL: CDR3 aa

<400> 64

Gln Gln Ser Tyr Ser Thr Pro Tyr Thr
1 5

<210> 65

<211> 357

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 VH: nuc

<400> 65
gagctgcagc tggtcgagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggccctgac 300

cgaatggggc atggttttga tatctggggc caagggacaa tggtcaccgt ctcctca 357

<210> 66

<211> 119

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 VH: aa

<400> 66

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

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

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

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

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

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

Arg Gly Pro Asp Arg Met Gly His Gly Phe Asp Ile Trp Gly Gln Gly
100 105 110

Thr Met Val Thr Val Ser Ser
115

<210> 67

<211> 15

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 VH: CDR1 nuc

<400> 67
ggttactact ggagc 15

<210> 68

<211> 5

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 VH: CDR1 aa

<400> 68

Gly Tyr Tyr Trp Ser
1 5

<210> 69

<211> 48

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 VH: CDR2 nuc

<400> 69
gaaatcaatc atagtggaag caccaactac aacccgtccc tcaagagt 48

<210> 70

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 VH: CDR2 aa

<400> 70

Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 71

<211> 33

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 VH: CDR3 nuc

<400> 71
ggccctgacc gaatggggca tggttttgat atc 33

<210> 72

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 VH: CDR3 aa

<400> 72

Gly Pro Asp Arg Met Gly His Gly Phe Asp Ile
1 5 10

<210> 73

<211> 321

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 VL: nuc

<400> 73

gagctccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaatca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagtag tctgcaacct 240

gaagattttg caacttatta ctgtcaacag agttacagta gcccgtggac attcggccaa 300

gggaccaagg tggagatcaa a 321

<210> 74

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 VL: aa

<400> 74

Glu Leu 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 Ser 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 Ser Pro Trp
85 90 95

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

<210> 75

<211> 33

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 VL: CDR1 nuc

<400> 75
cgggcaagtc agagcattag cagctattta aat 33

<210> 76

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 VL: CDR1 aa

<400> 76

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

<210> 77

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 VL: CDR2 nuc

<400> 77
gctgcatcca gtttgcaaag t 21

<210> 78

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 VL: CDR2 aa

<400> 78

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 79

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 VL: CDR3 nuc

<400> 79
caacagagtt acagtagccc g 21

<210> 80

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 VL: CDR3 aa

<400> 80

Gln Gln Ser Tyr Ser Ser Pro
1 5

<210> 81

<211> 381

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 VH: nuc

<400> 81

gagctgcagc tggtcgagtc tggtccagga ctggtgaagc cctcgcagac cctctcactc 60

acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg 120

cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180

aatgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240

cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300

agagatcgtc gacgtatagc agctcgtcaa tactacggta tggacgtctg gggccaaggg 360

accacggtca ccgtctcctc a 381

<210> 82

<211> 127

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 VH: aa

<400> 82

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

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

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

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

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

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Arg Arg Ile Ala Ala Arg Gln Tyr Tyr
100 105 110

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

<210> 83

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 VH: CDR1 nuc

<400> 83
agcaacagtg ctgcttggaa c 21

<210> 84

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 VH: CDR1 aa

<400> 84

Ser Asn Ser Ala Ala Trp Asn
1 5

<210> 85

<211> 54

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 VH: CDR2 nuc

<400> 85
aggacatact acaggtccaa gtggtataat gattatgcag tatctgtgaa aagt 54

<210> 86

<211> 18

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 VH: CDR2 aa

<400> 86

Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> 87

<211> 45

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 VH: CDR3 nuc

<400> 87
gatcgtcgac gtatagcagc tcgtcaatac tacggtatgg acgtc 45

<210> 88

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 VH: CDR3 aa

<400> 88

Asp Arg Arg Arg Ile Ala Ala Arg Gln Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 89

<211> 324

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 VL: nuc

<400> 89

gagctcgtgt tgacacagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggcaagtca gagtgttagc agcaactact tagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagcgg gtctgggaca gatttcactc tcaccatcag cagcctgcag 240

cctgaagatg ttgcaactta ttactgtcaa aagtataaca gtgcccctct cactttcggc 300

ggagggacca aggtggaaat caaa 324

<210> 90

<211> 108

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 VL: aa

<400> 90

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

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

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

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

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

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

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

<210> 91

<211> 36

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 VL: CDR1 nuc

<400> 91
agggcaagtc agagtgttag cagcaactac ttagcc 36

<210> 92

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 VL: CDR1 aa

<400> 92

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

<210> 93

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 VL: CDR2 nuc

<400> 93
ggtgcatcca gcagggccac t 21

<210> 94

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 VL: CDR2 aa

<400> 94

Gly Ala Ser Ser Arg Ala Thr
1 5

<210> 95

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 VL: CDR3 nuc

<400> 95
caaaagtata acagtgcccc t 21

<210> 96

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 VL: CDR3 aa

<400> 96

Gln Lys Tyr Asn Ser Ala Pro
1 5

<210> 97

<211> 363

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 VH: nuc

<400> 97
gagctgcagc tggtcgagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgggctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct gttagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagccaaa 300

ttcctgggcc actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360

tca 363

<210> 98

<211> 121

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 VH: aa

<400> 98

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

Ser Ala Val Ser Gly Ser Gly Gly Ser Thr 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 Ala Lys Phe Leu Gly His Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 99

<211> 15

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 VH: CDR1 nuc

<400> 99
agctatgcca tgggc 15

<210> 100

<211> 5

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 VH: CDR1 aa

<400> 100

Ser Tyr Ala Met Gly
1 5

<210> 101

<211> 51

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 VH: CDR2 nuc

<400> 101
gctgttagtg gtagtggtgg tagcacatac tacgcagact ccgtgaaggg c 51

<210> 102

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 VH: CDR2 aa

<400> 102

Ala Val Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 103

<211> 36

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 VH: CDR3 nuc

<400> 103
gccaaattcc tgggccacta ctacggtatg gacgtc 36

<210> 104

<211> 12

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 VH: CDR3 aa

<400> 104

Ala Lys Phe Leu Gly His Tyr Tyr Gly Met Asp Val
1 5 10

<210> 105

<211> 321

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 VL: nuc

<400> 105

gagctccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg agtcccatca 180

aggttcagcg gcagtggatc tgggacagag ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcttcag cataatgctt acccgtacac tttcggccag 300

gggaccaagg tggaaatcaa a 321

<210> 106

<211> 107

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 VL: aa

<400> 106

Glu Leu 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 Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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

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

<210> 107

<211> 33

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 VL: CDR1 nuc

<400> 107
cgggcaagtc agagcattag cagctattta aat 33

<210> 108

<211> 11

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 VL: CDR1 aa

<400> 108

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

<210> 109

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 VL: CDR2 nuc

<400> 109
gctgcatcca gtttgcaaag t 21

<210> 110

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 VL: CDR2 aa

<400> 110

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 111

<211> 27

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 VL: CDR3 nuc

<400> 111
cttcagcata atgcttaccc gtacact 27

<210> 112

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 VL: CDR3 aa

<400> 112

Leu Gln His Asn Ala Tyr Pro Tyr Thr
1 5

<210> 113

<211> 369

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 VH: nuc

<400> 113
gagctgcagc tggtcgagtc tggtcctgtg ctggtgaaac ccacagatac cctcacgctg 60

acttgcaccg tctctgggtt ctcactcaat aatcctagaa tgggtgtgag ctggatccgt 120

cagccccag ggaagaccct ggagtggctt gcacacattt ttccgagtga cgcaaaagcc 180

cacagtgcat ctctgaagag caggctcacc atctccaagg acacctccaa aagccaggtg 240

gtccctacca tgaccaacat ggaccctgtg gacacagcca catattactg tgcacggata 300

ttgggggaat actatccccc agcctggttc gacccctggg gccagggaac cctggtcacc 360

gtctcctca 369

<210> 114

<211> 123

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 VH: aa

<400> 114

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

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

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

Trp Leu Ala His Ile Phe Pro Ser Asp Ala Lys Ala His Ser Ala 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 Pro Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

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

<210> 115

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 VH: CDR1 nuc

<400> 115
aatcctagaa tgggtgtgag c 21

<210> 116

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 VH: CDR1 aa

<400> 116

Asn Pro Arg Met Gly Val Ser
1 5

<210> 117

<211> 48

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 VH: CDR2 nuc

<400> 117
cacatttttc cgagtgacgc aaaagcccac agtgcatctc tgaagagc 48

<210> 118

<211> 16

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 VH: CDR2 aa

<400> 118

His Ile Phe Pro Ser Asp Ala Lys Ala His Ser Ala Ser Leu Lys Ser
1 5 10 15

<210> 119

<211> 39

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 VH: CDR3 nuc

<400> 119
atattggggg aatactatcc cccagcctgg ttcgacccc 39

<210> 120

<211> 13

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 VH: CDR3 aa

<400> 120

Ile Leu Gly Glu Tyr Tyr Pro Pro Ala Trp Phe Asp Pro
1 5 10

<210> 121

<211> 339

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 VL: nuc

<400> 121
gagctcgtga tgacacagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60

atcaactgca agtccagcca gagtgtttta tacagctcca acaataagaa ctacttagct 120

tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctacccgg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240

atcagcagcc tgcaggctga agacgtggca gtttattact gtcagcaata tttgaaaatc 300

ccttatactt ttggccaggg gaccaaggtg gagatcaaa 339

<210> 122

<211> 113

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 VL: aa

<400> 122

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

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

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

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

Lys

<210> 123

<211> 51

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 VL: CDR1 nuc

<400> 123
aagtccagcc agagtgtttt atacagctcc aacaataaga actacttagc t 51

<210> 124

<211> 17

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 VL: CDR1 aa

<400> 124

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 125

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 VL: CDR2 nuc

<400> 125
tgggcatcta cccgggaatc c 21

<210> 126

<211> 7

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 VL: CDR2 aa

<400> 126

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 127

<211> 27

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 VL: CDR3 nuc

<400> 127
cagcaatatt tgaaaatccc ttatact 27

<210> 128

<211> 9

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 VL: CDR3 aa

<400> 128

Gln Gln Tyr Leu Lys Ile Pro Tyr Thr
1 5

<210> 129

<211> 372

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD19 VH: nuc

<400> 129
caggtgcagc tgcagcagtc tggggctgag ctggtgaggc ctgggtcctc agtgaagatt 60

tcctgcaagg cttctggcta tgcattcagt agctactgga tgaactgggt gaagcagagg 120

cctggacagg gtcttgagtg gattggacag atttggcctg gagatggtga tactaactac 180

aatggaaagt tcaagggtaa agccactctg actgcagacg aatcctccag cacagcctac 240

atgcaactca gcagcctagc atctgaggac tctgcggtct atttctgtgc aagacgggag 300

actacgacgg taggccgtta ttactatgct atggactact ggggccaagg gaccacggtc 360

accgtctcct cc 372

<210> 130

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD19 VH: aa

<400> 130

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

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

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

Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
50 55 60

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

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

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

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

<210> 131

<211> 333

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD19 VL: nuc

<400> 131
gatatccagc tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttattt gaactggtac 120

caacagattc caggacagcc acccaaactc ctcatctatg atgcatccaa tctagtttct 180

gggatcccac ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggaga aggtggatgc tgcaacctat cactgtcagc aaagtactga ggatccgtgg 300

acgttcggtg gagggaccaa gctcgagatc aaa 333

<210> 132

<211> 111

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD19 VL: aa

<400> 132

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

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

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35 40 45

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

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

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

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 133

<211> 360

<212> DNA

<213> artificial sequence

<220>

<223> anti-EpCAM (5-10) VH: nuc

<400> 133

gaggtgcagc tgctcgagca gtctggagct gagctggtaa ggcctgggac ttcagtgaag 60

atatcctgca aggcttctgg atacgccttc actaactact ggctaggttg ggtaaagcag 120

aggcctggac atggacttga gtggattgga gatattttcc ctggaagtgg taatatccac 180

tacaatgaga agttcaaggg caaagccaca ctgactgcag acaaatcttc gagcacagcc 240

tatatgcagc tcagtagcct gacatttgag gactctgctg tctatttctg tgcaagactg 300

aggaactggg acgagcctat ggactactgg ggccaaggga ccacggtcac cgtctcctca 360

<210> 134

<211> 120

<212> PRT

<213> artificial sequence

<220>

<223> anti-EpCAM (5-10) VH: aa

<400> 134

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

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

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

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

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

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

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 135

<211> 339

<212> DNA

<213> artificial sequence

<220>

<223> anti-EpCAM (5-10) VL: nuc

<400> 135
gagctcgtga tgacacagtc tccatcctcc ctgactgtga cagcaggaga gaaggtcact 60

atgagctgca agtccagtca gagtctgtta aacagtggaa atcaaaagaa ctacttgacc 120

tggtaccagc agaaaccagg gcagcctcct aaactgttga tctactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240

atcagcagtg tgcaggctga agacctggca gtttattact gtcagaatga ttatagttat 300

ccgctcacgt tcggtgctgg gaccaagctt gagatcaaa 339

<210> 136

<211> 113

<212> PRT

<213> artificial sequence

<220>

<223> anti-EpCAM (5-10) VL: aa

<400> 136

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 137

<211> 36

<212> DNA

<213> artificial sequence

<220>

<223> 5' BsrGI primer

<400> 137
aggtgtacac tccgatggta atgaagaaat gggtgg 36

<210> 138

<211> 42

<212> DNA

<213> artificial sequence

<220>

<223> 3' BspEI primer

<400> 138
cgatccggaa tccatctcca tgcagttctc acacactctt gc 42

<210> 139

<211> 146

<212> DNA

<213> artificial sequence

<220>

<223> mouse Ig leader and cloning site

<400> 139
gaattcacca tgggatggag ctgtatcatc ctcttcttgg tagcaacagc tacaggtgta 60

cactccgata tcaagcttcc ggacgctccc gactcaagcg cccgtgccac acagccgcaa 120

gatctggcgc cgtgtggtca gtcgac 146

<210> 140

<211> 393

<212> DNA

<213> artificial sequence

<220>

<223> CD3-epsilon extracellular domain with leader

<400> 140

atgggatgga gctgtatcat cctcttcttg gtagcaacag ctacaggtgt acactccgat 60

ggtaatgaag aaatgggtgg tattacacag acaccatata aagtctccat ctctggaacc 120

acagtaatat tgacatgccc tcagtatcct ggatctgaaa tactatggca acacaatgat 180

aaaaacatag gcggtgatga ggatgataaa aacataggca gtgatgagga tcacctgtca 240

ctgaaggaat tttcagaatt ggagcaaagt ggttattatg tctgctaccc cagaggaagc 300

aaaccagaag atgcgaactt ttatctctac ctgagggcaa gagtgtgtga gaactgcatg 360

gagatggatt ccgggcatca tcaccatcat cat 393

<210> 141

<211> 131

<212> PRT

<213> artificial sequence

<220>

<223> translation of CD3-epsilon extracellular domain with leader

<400> 141

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Asp Gly Asn Glu Glu Met Gly Gly Ile Thr Gln Thr Pro
20 25 30

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

Tyr Pro Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys Asn Ile Gly
50 55 60

Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp His Leu Ser
65 70 75 80

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

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

Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Ser Gly His His His
115 120 125

His His His
130

<210> 142

<211> 22

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVH1,3,5-XhoI-2001

<400> 142
aggtgcagct gctcgagtct gg 22

<210> 143

<211> 23

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVH2-XhoI-2001

<400> 143
cagrtcacct tgctcgagtc tgg 23

<210> 144

<211> 23

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVH4-XhoI-2001

<400> 144
caggtgcagc tgctcgagtc ggg 23

<210> 145

<211> 23

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVH4B-XhoI-2001

<400> 145
caggtgcagc tactcgagtg ggg 23

<210> 146

<211> 23

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVH6-XhoI-2001

<400> 146
caggtacagc tgctcgagtc agg 23

<210> 147

<211> 30

<212> DNA

<213> artificial sequence

<220>

<223> 3'-CD1

<400> 147
tgccttacta gtctctggcc agcggaagat 30

<210> 148

<211> 17

<212> DNA

<213> artificial sequence

<220>

<223> 3'-hu-VH-BstEII-2001

<400> 148
ctgaggagac ggtgacc 17

<210> 149

<211> 17

<212> DNA

<213> artificial sequence

<220>

<223> 3'-hu-VH-J3-BstEII

<400> 149
ctgaagagac ggtgacc 17

<210> 150

<211> 38

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVK1-Sac-2001

<400> 150
gagccgcacg agcccgagct ccagatgacc cagtctcc 38

<210> 151

<211> 38

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVK3-Sac-2001

<400> 151
gagccgcacg agcccgagct cgtgwtgacr cagtctcc 38

<210> 152

<211> 38

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVK2/4-Sac-2001

<400> 152
gagccgcacg agcccgagct cgtgatgacy cagtctcc 38

<210> 153

<211> 38

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVK5-Sac-2001

<400> 153
gagccgcacg agcccgagct cacactcacg cagtctcc 38

<210> 154

<211> 38

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVK6-Sac-2001

<400> 154
gagccgcacg agcccgagct cgtgctgact cagtctcc 38

<210> 155

<211> 47

<212> DNA

<213> artificial sequence

<220>

<223> 3'-hu-Vk-J1-SpeI-BsiWI

<400> 155
gacgacacta gttgcagcca ccgtacgttt gatttccacc ttggtcc 47

<210> 156

<211> 47

<212> DNA

<213> artificial sequence

<220>

<223> 3'-hu-Vk-J2/4-SpeI-BsiWI

<400> 156
gacgacacta gttgcagcca ccgtacgttt gatctccasc ttggtcc 47

<210> 157

<211> 47

<212> DNA

<213> artificial sequence

<220>

<223> 3'-hu-Vk-J3-SpeI-BsiWI

<400> 157
gacgacacta gttgcagcca ccgtacgttt gatatccacg ttggtcc 47

<210> 158

<211> 47

<212> DNA

<213> artificial sequence

<220>

<223> 3'-hu-Vk-J5-SpeI-BsiWI

<400> 158
gacgacacta gttgcagcca ccgtacgttt aatctccagt cgtgtcc 47

<210> 159

<211> 41

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVL1a-SacI-2001

<400> 159
gagccgcacg agcccgagct cgtgttgacg cagccgccct c 41

<210> 160

<211> 41

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVL1b-SacI-2001

<400> 160
gagccgcacg agcccgagct cgtgctgact cagccaccct c 41

<210> 161

<211> 44

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVL2-SacI-2001

<400> 161
gagccgcagg agcccgagct cgccctgact cagcctscct ccgt 44

<210> 162

<211> 35

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVL4-SacI-2001

<400> 162
acctgcgagc tcgtgctgac tcarycmycc tctgc 35

<210> 163

<211> 33

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVL5-SacI-2001

<400> 163
acctgcgagc tcgtgctgac tcagccrsct tcc 33

<210> 164

<211> 32

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVL6-SacI-2001

<400> 164
acctgcgagc tcatgctgac tcagccccac tc 32

<210> 165

<211> 41

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVL3/9-SacI-2001

<400> 165
gagccgcacg agcccgagct cgwgctgact cagccaccyt c 41

<210> 166

<211> 41

<212> DNA

<213> artificial sequence

<220>

<223> 5'-huVL7/8-SacI-2001

<400> 166
gagccgcacg agcccgagct cgtggtgacy caggagccmt c 41

<210> 167

<211> 33

<212> DNA

<213> artificial sequence

<220>

<223> 3'-hu-Vlam-BlnI-SpeI-2001

<400> 167
cgtgggacta gtcttgggct gacctaggac ggt 33

<210> 168

<211> 33

<212> DNA

<213> artificial sequence

<220>

<223> 3'-hu-Vlam2-BlnI-SpeI-2002

<400> 168
cgtgggacta gtcttgggct gaccgaggac ggt 33

<210> 169

<211> 36

<212> DNA

<213> artificial sequence

<220>

<223> 5`-Mouse ckappa BsiWI

<400> 169
actcgacgta cggatgctgc accaactgta tccatc 36

<210> 170

<211> 58

<212> DNA

<213> artificial sequence

<220>

<223> 3'-Mouse-ck-myc

<400> 170
cagatcttcc tctgagatca gcttctgttc ctcacactca ttcctgttga agctcttg 58

<210> 171

<211> 68

<212> DNA

<213> artificial sequence

<220>

<223> 3'-myc-His6-Not

<400> 171
tcagtagcgg ccgcttaatg gtgatggtgg tgatgcagat cttcctctga gatcagcttc 60

tgttcctc 68

<210> 172

<211> 34

<212> DNA

<213> artificial sequence

<220>

<223> 5'-5BVH-BsrGI

<400> 172
acgtcatgta cactccgagg tgcagctgct cgag 34

<210> 173

<211> 35

<212> DNA

<213> artificial sequence

<220>

<223> 3'-5BVL-BspEI

<400> 173
tgcatgtccg gacgtacgtt tgatctcaag cttgg 35

<210> 174

<211> 45

<212> DNA

<213> artificial sequence

<220>

<223> (G4S)3 linker nuc

<400> 174
ggtggtggtg gttctggcgg cggcggctcc ggtggtggtg gttct 45

<210> 175

<211> 15

<212> PRT

<213> artificial sequence

<220>

<223> (G4S)3 linker aa

<400> 175

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 176

<211> 15

<212> DNA

<213> artificial sequence

<220>

<223> (G4S)1 linker nuc

<400> 176
ggaggtggtg gatcc 15

<210> 177

<211> 5

<212> PRT

<213> artificial sequence

<220>

<223> (G4S)1 linker aa

<400> 177

Gly Gly Gly Gly Ser
1 5

<210> 178

<211> 383

<212> DNA

<213> artificial sequence

<220>

<223> mouse ckappa-myc-his6

<400> 178
cgtacggatg ctgcaccaac tgtatccatc ttcccaccat ccagtgagca gttaacatct 60

ggaggtgcct cagtcgtgtg cttcttgaac aacttctacc ccaaagacat caatgtcaag 120

tggaagattg atggcagtga acgacaaaat ggcgtcctga acagttggac tgatcaggac 180

agcaaagaca gcacctacag catgagcagc accctcacgt tgaccaagga cgagtatgaa 240

cgacataaca gctatacctg tgaggccact cacaagacat caacttcacc cattgtcaag 300

agcttcaaca ggaatgagtg tgaggaacag aagctgatct cagaggaaga tctgcatcac 360

caccatcacc attaagcggc cgc 383

<210> 179

<211> 124

<212> PRT

<213> artificial sequence

<220>

<223> translation of mouse ckappa-myc-his6

<400> 179

Arg Thr Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
1 5 10 15

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

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
35 40 45

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
65 70 75 80

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
85 90 95

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys Glu Glu Gln Lys Leu
100 105 110

Ile Ser Glu Glu Asp Leu His His His His His His
115 120

<210> 180

<211> 741

<212> DNA

<213> artificial sequence

<220>

<223> 3-106 nuc

<400> 180
gagctgcagc tggtcgagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatcatatg atggaagtaa taaatactac 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag atctgaggac acggccgtgt attactgtgc gaggctcagc 300

ccgtattgta ctaatggtgt atgctgggat gcttttgata tctggggcca agggacaatg 360

gtcaccgtct cctcaggtgg tggtggttct ggcggcggcg gctccggtgg tggtggttct 420

gagctccaga tgacccagtc tccatcctcc ctgtctgcat ctgtcggaga cagagtctcc 480

atcacttgtc gggcaagtca gaccattagc aattatttaa attggtatca actgaagcca 540

gggaaagccc ctaagctcct gatctatgct gcatccactt tgcaaagtga ggtcccaacc 600

aggttcagtg gcagtgggtc tgggacagat ttcactctca ccatcagtgg tctgcatcct 660

gaagattttg caacttacta ctgtcaacag tttaatagtt atcctcgaac gttcggccaa 720

gggaccaagg tggaaatcaa a 741

<210> 181

<211> 247

<212> PRT

<213> artificial sequence

<220>

<223> 3-106 aa

<400> 181

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

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

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

Ala Val Ile Ser Tyr Asp Gly Ser Asn 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 Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Leu Ser Pro Tyr Cys Thr Asn Gly Val Cys Trp Asp Ala Phe
100 105 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Gln Met
130 135 140

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Ser

145 150 155 160

Ile Thr Cys Arg Ala Ser Gln Thr Ile Ser Asn Tyr Leu Asn Trp Tyr
165 170 175

Gln Leu Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser
180 185 190

Thr Leu Gln Ser Glu Val Pro Thr Arg Phe Ser Gly Ser Gly Ser Gly
195 200 205

Thr Asp Phe Thr Leu Thr Ile Ser Gly Leu His Pro Glu Asp Phe Ala
210 215 220

Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Arg Thr Phe Gly Gln
225 230 235 240

Gly Thr Lys Val Glu Ile Lys
245

<210> 182

<211> 732

<212> DNA

<213> artificial sequence

<220>

<223> 3-114 nuc

<400> 182

gagctgcagc tggtcgagtc tgggggaggc ttggtaaagc agggcggtc cctgagactc 60

tcctgtacag cttctggatt cacctttggt gattatgcta tgagctggtt ccgccaggct 120

ccagggaagg ggctggagtg ggtaggtttc attagaagca aagcttatgg tgggacaaca 180

gaatacgccg cgtctgtgaa aggcagattc accatctcaa gagatgattc caaaagcatc 240

gcctatctgc aaatgaacag cctgaaaacc gaggacacag ccgtgtatta ctgtactcca 300

cagctatggt tactacaaga tgcttttgat atctggggcc aagggacaat ggtcaccgtc 360

tcctcaggtg gtggtggttc tggcggcggc ggctccggtg gtggtggttc tgagctccag 420

atgacccagt ctccatcctc cctgtctgca tctgtaggag atagagtcac catcacttgc 480

cgggcgagtc agggcattag caattattta gcctggtatc agcagaaacc agggaaagtt 540

cctaagctcc tgatctatgc tgcatccact ttgcaatcag gggtcccatc tcggttcagt 600

ggcagtggat ctgggacaga tttcactctc accatcagca gtctgcaacc tgaagatttt 660

gcaacttact actgtcaaca gagttacagt acccctccga cgttcggcca agggaccaag 720

ctggagatca aa 732

<210> 183

<211> 244

<212> PRT

<213> artificial sequence

<220>

<223> 3-114 aa

<400> 183

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

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

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

Gly Phe Ile Arg Ser Lys Ala Tyr Gly Gly Thr Thr Glu Tyr Ala Ala
50 55 60

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

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

Tyr Cys Thr Pro Gln Leu Trp Leu Leu Gln Asp Ala Phe Asp Ile Trp
100 105 110

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Gln Met Thr Gln Ser
130 135 140

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

Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
165 170 175

Pro Gly Lys Val Pro Lys Leu Leu Ile Tyr Ala Ala Ser Thr Leu Gln
180 185 190

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
195 200 205

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr

210 215 220

Cys Gln Gln Ser Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys
225 230 235 240

Leu Glu Ile Lys

<210> 184

<211> 726

<212> DNA

<213> artificial sequence

<220>

<223> 3-148 nuc

<400> 184
gagctgcagc tggtcgagtc tggcccagga ctggtgaagc cttcggggac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtagaaact ggtggagttg ggtccgccag 120

cccccaggga aggggctgga gtggattggt gatatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagtgggtat 300

accagctgtc gtgatgcttt tgatatctgg ggccaaggga caatggtcac cgtctcctca 360

ggtggtggtg gttctggcgg cggcggctcc ggtggtggtg gttctgagct cgtgatgact 420

cagtctccat cctccctgtc tgcatctgta ggagacagag tcaccatcac ttgccgggcg 480

agtcagggca ttggcaatta tttagcctgg tatcagcaga aaccagggca gcctcctaag 540

atgctcattt actgggcatc aatccgggaa tccggggtcc ctgaccgatt cagtggcagc 600

gggtctggga cagacttcac tctcaccatc agcagcctgc aggctgaaga tgtggcagtt 660

tactactgtc agcaatatta tagtaatcct cagacgttcg gccaagggac caaggtggaa 720

atcaaa 726

<210> 185

<211> 242

<212> PRT

<213> artificial sequence

<220>

<223> 3-148 aa

<400> 185

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Glu Leu Gln Leu Val 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 Ser Ser Arg
            20                  25                  30

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

Ile Gly Asp Ile Tyr His Ser 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 Gln 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 Ser Gly Tyr Thr Ser Cys Arg Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Ser Gln Gly Ile Gly Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Gln Pro Pro Lys Met Leu Ile Tyr Trp Ala Ser Ile Arg Glu Ser Gly
            180                 185                 190

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
    210                 215                 220

Gln Tyr Tyr Ser Asn Pro Gln Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys
```

<210> 186

<211> 744

<212> DNA

<213> artificial sequence

<220>

<223> 3-190 nuc

<400> 186

gagctgcagc tggtcgagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggccgaggc 300

cgatttttgg ggtggttatt aggggggctcc aactggttcg acccctgggg ccagggaacc 360

ctggtcaccg tctcctcagg tggtggtggt tctggcggcg gcggctccgg tggtggtggt 420

tctgagctcg tgatgaccca gtctccatcc tccctgtctg catctgtagg agacagagtc 480

accatcactt gccgggcgag tcagggcatt agcaattatt taaattggta tcagcagaaa 540

ccagggaaag cccctaagct cctgatctac gatgcatcca atttggaaac aggggtccca 600

tcaaggttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagtctgcaa 660

cctgaagatt ttgcaactta ctactgtcaa cagagttaca gtaccccgta cacttttggc 720

caggggacca aagtggatat caaa 744

<210> 187

<211> 248

<212> PRT

<213> artificial sequence

<220>

<223> 3-190 aa

<400> 187

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

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

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

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

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

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

Arg Gly Arg Gly Arg Phe Leu Gly Trp Leu Leu Gly Gly Ser Asn Trp
100 105 110

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

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val
130 135 140

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
145 150 155 160

Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Asn Trp
165 170 175

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala
180 185 190

Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
195 200 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
210 215 220

Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr Thr Phe Gly
225 230 235 240

Gln Gly Thr Lys Val Asp Ile Lys
245

<210> 188

<211> 723

<212> DNA

<213> artificial sequence

<220>

<223> 3-271 nuc

<400> 188
gagctgcagc tggtcgagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggccctgac 300

cgaatggggc atggttttga tatctggggc caagggacaa tggtcaccgt ctcctcaggt 360

ggtggtggtt ctggcggcgg cggctccggt ggtggtggtt ctgagctcca gatgacccag 420

tctccatcct ccctgtctgc atctgtagga gacagagtca ccatcacttg ccgggcaagt 480

cagagcatta gcagctattt aaattggtat cagcagaaat cagggaaagc ccctaagctc 540

ctgatctatg ctgcatccag tttgcaaagt ggggtcccat caaggttcag tggcagtgga 600

tctgggacag atttcactct caccatcagt agtctgcaac ctgaagattt tgcaacttat 660

tactgtcaac agagttacag tagcccgtgg acattcggcc aagggaccaa ggtggagatc 720

aaa 723

<210> 189

<211> 241

<212> PRT

<213> artificial sequence

<220>

<223> 3-271 aa

<400> 189

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

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

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

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

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

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

Arg Gly Pro Asp Arg Met Gly His Gly Phe Asp Ile Trp Gly Gln Gly
100 105 110

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

Ser Gly Gly Gly Gly Ser Glu Leu Gln Met Thr Gln Ser Pro Ser Ser
130 135 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145 150 155 160

Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Ser Gly Lys
165 170 175

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
180 185 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
195 200 205

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
210 215 220

Ser Tyr Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
225 230 235 240

Lys

<210> 190

<211> 750

<212> DNA

<213> artificial sequence

<220>

<223> 3-550 nuc

<400> 190
gagctgcagc tggtcgagtc tggtccagga ctggtgaagc cctcgcagac cctctcactc 60

acctgtgcca tctccgggga cagtgtctct agcaacagtg ctgcttggaa ctggatcagg 120

cagtccccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtggtat 180

aatgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240

cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300

agagatcgtc gacgtatagc agctcgtcaa tactacggta tggacgtctg gggccaaggg 360

accacggtca ccgtctcctc aggtggtggt ggttctggcg gcggcggctc cggtggtggt 420

ggttctgagc tcgtgttgac acagtctcca ggcaccctgt ctttgtctcc aggggaaaga 480

gccaccctct cctgcagggc aagtcagagt gttagcagca actacttagc ctggtaccag 540

cagaaacctg gccaggctcc caggctcctc atctatggtg catccagcag ggccactggc 600

atcccagaca ggttcagtgg cagcgggtct gggacagatt tcactctcac catcagcagc 660

ctgcagcctg aagatgttgc aacttattac tgtcaaaagt ataacagtgc ccctctcact 720

ttcggcggag ggaccaaggt ggaaatcaaa 750

<210> 191

<211> 250

<212> PRT

<213> artificial sequence

<220>

<223> 3-550 aa

<400> 191

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

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

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

Trp Leu Gly Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala
50 55 60

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

Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val
85 90 95

Tyr Tyr Cys Ala Arg Asp Arg Arg Arg Ile Ala Ala Arg Gln Tyr Tyr
100 105 110

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

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu
130 135 140

Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly Glu Arg
145 150 155 160

Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn Tyr Leu
165 170 175

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr
180 185 190

Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser Gly Ser
195 200 205

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
210 215 220

Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Leu Thr
225 230 235 240

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
245 250

<210> 192

<211> 729

<212> DNA

<213> artificial sequence

<220>

<223> 4-10 nuc

<400> 192
gagctgcagc tggtcgagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgggctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct gttagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagccaaa 300

ttcctgggcc actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360

tcaggtggtg gtggttctgg cggcggcggc tccggtggtg gtggttctga gctccagatg 420

acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccgg 480

gcaagtcaga gcattagcag ctatttaaat tggtatcagc agaaaccagg gaaagcccct 540

aagctcctga tctatgctgc atccagtttg caaagtggag tcccatcaag gttcagcggc 600

agtggatctg ggacagagtt cactctcaca atcagcagcc tgcagcctga agattttgca 660

acttattact gtcttcagca taatgcttac ccgtacactt tcggccaggg gaccaaggtg 720

gaaatcaaa 729

<210> 193

<211> 243

<212> PRT

<213> artificial sequence

<220>

<223> 4-10 aa

<400> 193

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

Ser Ala Val Ser Gly Ser Gly Gly Ser Thr 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 Ala Lys Phe Leu Gly His Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110

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

Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Gln Met Thr Gln Ser Pro
130 135 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145 150 155 160

Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Leu Gln His Asn Ala Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys

<210> 194

<211> 753

<212> DNA

<213> artificial sequence

<220>

<223> 4-48 nuc

<400> 194

gagctgcagc tggtcgagtc tggtcctgtg ctggtgaaac ccacagatac cctcacgctg 60

acttgcaccg tctctgggtt ctcactcaat aatcctagaa tgggtgtgag ctggatccgt 120

cagcccccag ggaagaccct ggagtggctt gcacacattt ttccgagtga cgcaaaagcc 180

cacagtgcat ctctgaagag caggctcacc atctccaagg acacctccaa aagccaggtg 240

gtccctacca tgaccaacat ggaccctgtg gacacagcca catattactg tgcacggata 300

ttgggggaat actatccccc agcctggttc gacccctggg gccagggaac cctggtcacc 360

gtctcctcag gtggtggtgg ttctggcggc ggcggctccg gtggtggtgg ttctgagctc 420

gtgatgacac agtctccaga ctccctggct gtgtctctgg gcgagagggc caccatcaac 480

tgcaagtcca gccagagtgt tttatacagc tccaacaata agaactactt agcttggtac 540

cagcagaaac caggacagcc tcctaagctg ctcatttact gggcatctac ccgggaatcc 600

ggggtccctg accgattcag tggcagcggg tctgggacag atttcactct caccatcagc 660

agcctgcagg ctgaagacgt ggcagtttat tactgtcagc aatatttgaa aatccccttat 720

acttttggcc aggggaccaa ggtggagatc aaa 753

<210> 195

<211> 251

<212> PRT

<213> artificial sequence

<220>

<223> 4-48 aa

<400> 195

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

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

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

Trp Leu Ala His Ile Phe Pro Ser Asp Ala Lys Ala His Ser Ala 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 Pro Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

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

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln
130 135 140

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
145 150 155 160

Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
165 170 175

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
180 185 190

Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
195 200 205

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
210 215 220

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Leu Lys Ile Pro Tyr
225 230 235 240

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
245 250

<210> 196

<211> 354

<212> DNA

<213> artificial sequence

<220>

<223> anti-CCR5 VH nuc

<400> 196
cagctggagc agtctggacc tgaactgaag aagcctggag agacagtcac gatctcctgc 60

aaggcttctg ggtatacctt cacgaagttc ggaatgaact gggtgaagca ggctccagga 120

aagggtttaa agtggatggg ctggatacac acctccactg gagagccaac atattctgat 180

gacttcaagg gacggtttgc cttctctttg gaaacgtctg ccagcactgc ctatttgcgg 240

atcaacaacc tcaaaaatga ggacatggct aaatacttct gtgccagagg tggtccttac 300

gtaaggggtg ctttggacta ctggggtcaa ggaacctcag tcaccgtctc ctcc 354

<210> 197

<211> 118

<212> PRT

<213> artificial sequence

<220>

<223> anti-CCR5 VH aa

<400> 197

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

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

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

Ile His Thr Ser Thr Gly Glu Pro Thr Tyr Ser Asp Asp Phe Lys Gly
50 55 60

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

Ile Asn Asn Leu Lys Asn Glu Asp Met Ala Lys Tyr Phe Cys Ala Arg
85 90 95

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

Ser Val Thr Val Ser Ser
115

<210> 198

<211> 333

<212> DNA

<213> artificial sequence

<220>

<223> anti-CCR5 VL nuc

<400> 198
gacattatcc tgatccaatc tccaccttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca gaaccagcga aaatgttgac ggatacggca ttagttttat aaactggtac 120

caacagaagc caggacagcc acccaaactc ctcatctatg ctgcatccca ccaaggatcc 180

ggggtccctg ccagatttag tggcagtggg tctgggacag acttcagcct caacatccat 240

cctttggagg aggatgatac tgcaatgtat ttctgtcacc aaagtaagaa ggttccgtgg 300

acgttcggtg gaggcaccaa gctggaaatc aaa 333

<210> 199

<211> 111

<212> PRT

<213> artificial sequence

<220>

<223> anti-CCR5 VL aa

<400> 199

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

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

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

Lys Leu Leu Ile Tyr Ala Ala Ser His Gln Gly Ser Gly Val Pro Ala
50 55 60

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

Pro Leu Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys His Gln Ser Lys
85 90 95

Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 200

<211> 366

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD20 VH: nuc

<400> 200

caggtgcaac tgcggcagcc tggggctgag ctggtgaagc ctggggcctc agtgaagatg 60

tcctgcaagg cttctggcta cacatttacc agttacaata tgcactgggt aaagcagaca 120

cctggacagg gcctggaatg gattggagct atttatccag gaaatggtga tacttcctac 180

aatcagaagt tcaaaggcaa ggccacattg actgcagaca aatcctccag cacagcctac 240

atgcagctca gcagtctgac atctgaggac tctgcggtct attactgtgc aagatcgcac 300

tacggtagta actacgtaga ctactttgac tactggggcc aaggcacact agtcacagtc 360

tcgaca 366

<210> 201

<211> 122

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD20 VH: aa

<400> 201

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

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

Asn Met His Trp Val Lys Gln Thr Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Ser His Tyr Gly Ser Asn Tyr Val Asp Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Thr

115 120

<210> 202

<211> 318

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD20 VL: nuc

<400> 202

caaattgttc tctcccagtc tccagcaatc ctttctgcat ctccagggga gaaggtcaca 60

atgacttgca gggccagctc aagtttaagt ttcatgcact ggtaccagca gaagccagga 120

tcctcccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa 240

gatgctgcca cttatttctg ccatcagtgg agtagtaacc cgctcacgtt cggtgctggg 300

acaaaggtgg aaataaaa 318

<210> 203

<211> 106

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD20 VL:aa

<400> 203

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Leu Ser Phe Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

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

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

Asp Ala Ala Thr Tyr Phe Cys His Gln Trp Ser Ser Asn Pro Leu Thr
85 90 95

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

<210> 204

<211> 21

<212> DNA

<213> artificial sequence

<220>

<223> leader seq

<400> 204
cctcttcttg gtagcaacag c 21

<210> 205

<211> 1491

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 3-148 VH-VL x anti-CD19 VL-VH

<400> 205
gagctgcagc tggtcgagtc tggcccagga ctggtgaagc cttcggggac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtagaaact ggtggagttg ggtccgccag 120

cccccaggga aggggctgga gtggattggt gatatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagtgggtat 300

accagctgtc gtgatgcttt tgatatctgg ggccaaggga caatggtcac cgtctcctca 360

ggtggtggtg gttctggcgg cggcggctcc ggtggtggtg gttctgagct cgtgatgact 420

cagtctccat cctccctgtc tgcatctgta ggagacagag tcaccatcac ttgccgggcg 480

agtcagggca ttggcaatta tttagcctgg tatcagcaga aaccagggca gcctcctaag 540

atgctcattt actgggcatc aatccgggaa tccggggtcc ctgaccgatt cagtggcagc 600

gggtctggga cagacttcac tctcaccatc agcagcctgc aggctgaaga tgtggcagtt 660

tactactgtc agcaatatta tagtaatcct cagacgttcg gccaagggac caaggtggaa 720

atcaaaggag gtggtggatc cgatatccag ctgacccagt ctccagcttc tttggctgtg 780

tctctagggc agagggccac catctcctgc aaggccagcc aaagtgttga ttatgatggt 840

gatagttatt tgaactggta ccaacagatt ccaggacagc cacccaaact cctcatctat 900

gatgcatcca atctagtttc tgggatccca cccaggttta gtggcagtgg gtctgggaca 960

gacttcaccc tcaacatcca tcctgtggag aaggtggatg ctgcaaccta tcactgtcag 1020

caaagtactg aggatccgtg gacgttcggt ggagggacca agctcgagat caaaggtggt 1080

ggtggttctg gcggcggcgg ctccggtggt ggtggttctc aggtgcagct gcagcagtct 1140

ggggctgagc tggtgaggcc tgggtcctca gtgaagattt cctgcaaggc ttctggctat 1200

gcattcagta gctactggat gaactgggtg aagcagaggc ctggacaggg tcttgagtgg 1260

attggacaga tttggcctgg agatggtgat actaactaca atggaaagtt caagggtaaa 1320

gccactctga ctgcagacga atcctccagc acagcctaca tgcaactcag cagcctagca 1380

tctgaggact ctgcggtcta tttctgtgca agacgggaga ctacgacggt aggccgttat 1440

tactatgcta tggactactg gggccaaggg accacggtca ccgtctcctc c 1491

<210> 206

<211> 497

<212> PRT

<213> artificial sequence

<220>

<223> Human anti-CD3 3-148 VH-VL x anti-CD19 VL-VH

<400> 206

Glu Leu Gln Leu Val 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 Ser Ser Arg
20 25 30

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

Ile Gly Asp Ile Tyr His Ser 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 Gln 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 Ser Gly Tyr Thr Ser Cys Arg Asp Ala Phe Asp Ile Trp Gly Gln
100 105 110

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

Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser Pro Ser
130 135 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145 150 155 160

Ser Gln Gly Ile Gly Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
165 170 175

Gln Pro Pro Lys Met Leu Ile Tyr Trp Ala Ser Ile Arg Glu Ser Gly
180 185 190

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
195 200 205

Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
210 215 220

Gln Tyr Tyr Ser Asn Pro Gln Thr Phe Gly Gln Gly Thr Lys Val Glu
225 230 235 240

Ile Lys Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ala
245 250 255

Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala
260 265 270

Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr Gln
275 280 285

Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn
290 295 300

Leu Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr
305 310 315 320

Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala Thr
325 330 335

Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly
340 345 350

Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
355 360 365

Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu
370 375 380

Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr
385 390 395 400

Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln

405 410 415

Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn
420 425 430

Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser
435 440 445

Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser
450 455 460

Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr
465 470 475 480

Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
485 490 495

Ser

<210> 207

<211> 1509

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 3-190 VH-VL x anti-CD19 VL-VH

<400> 207

gagctgcagc tggtcgagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggccgaggc 300

cgatttttgg ggtggttatt aggggctcc aactggttcg acccctgggg ccagggaacc 360

ctggtcaccg tctcctcagg tggtggtggt tctggcggcg gcggctccgg tggtggtggt 420

tctgagctcg tgatgaccca gtctccatcc tccctgtctg catctgtagg agacagagtc 480

accatcactt gccgggcgag tcagggcatt agcaattatt taaattggta tcagcagaaa 540

ccagggaaag cccctaagct cctgatctac gatgcatcca atttggaaac aggggtccca 600

tcaaggttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagtctgcaa 660

cctgaagatt ttgcaactta ctactgtcaa cagagttaca gtaccccgta cacttttggc 720

caggggacca aagtggatat caaaggaggt ggtggatccg atatccagct gacccagtct 780

ccagcttctt tggctgtgtc tctagggcag agggccacca tctcctgcaa ggccagccaa 840

agtgttgatt atgatggtga tagttatttg aactggtacc aacagattcc aggacagcca 900

cccaaactcc tcatctatga tgcatccaat ctagtttctg ggatcccacc caggtttagt 960

ggcagtgggt ctgggacaga cttcaccctc aacatccatc ctgtggagaa ggtggatgct 1020

gcaacctatc actgtcagca aagtactgag gatccgtgga cgttcggtgg agggaccaag 1080

ctcgagatca aaggtggtgg tggttctggc ggcggcggct ccggtggtgg tggttctcag 1140

gtgcagctgc agcagtctgg ggctgagctg gtgaggcctg ggtcctcagt gaagatttcc 1200

tgcaaggctt ctggctatgc attcagtagc tactggatga actgggtgaa gcagaggcct 1260

ggacagggtc ttgagtggat tggacagatt tggcctggag atggtgatac taactacaat 1320

ggaaagttca agggtaaagc cactctgact gcagacgaat cctccagcac agcctacatg 1380

caactcagca gcctagcatc tgaggactct gcggtctatt tctgtgcaag acgggagact 1440

acgacggtag gccgttatta ctatgctatg gactactggg gccaagggac cacggtcacc 1500

gtctcctcc 1509

<210> 208

<211> 503

<212> PRT

<213> artificial sequence

<220>

<223> Human anti-CD3 3-190 VH-VL x anti-CD19 VL-VH

<400> 208

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

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

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

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

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

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

Arg Gly Arg Gly Arg Phe Leu Gly Trp Leu Leu Gly Gly Ser Asn Trp
100 105 110

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

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val
    130                 135                 140

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
145                 150                 155                 160

Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Asn Trp
                165                 170                 175

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala
            180                 185                 190

Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
        195                 200                 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
    210                 215                 220

Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr Thr Phe Gly
225                 230                 235                 240

Gln Gly Thr Lys Val Asp Ile Lys Gly Gly Gly Gly Ser Asp Ile Gln
                245                 250                 255

Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala
            260                 265                 270

Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser
        275                 280                 285

Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu
    290                 295                 300

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

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu
                325                 330                 335

Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro
            340                 345                 350

Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly
        355                 360                 365

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln
    370                 375                 380
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Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser
385 390 395 400

Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val
405 410 415

Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro
420 425 430

Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr
435 440 445

Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser
450 455 460

Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr
465 470 475 480

Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly
485 490 495

Thr Thr Val Thr Val Ser Ser
500

<210> 209

<211> 1488

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 3-271 VH-VL x anti-CD19 VL-VH

<400> 209

gagctgcagc tggtcgagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggccctgac 300

cgaatggggc atggttttga tatctggggc caagggacaa tggtcaccgt ctcctcaggt 360

ggtggtggtt ctggcggcgg cggctccggt ggtggtggtt ctgagctcca gatgacccag 420

tctccatcct ccctgtctgc atctgtagga gacagagtca ccatcacttg ccgggcaagt 480

cagagcatta gcagctattt aaattggtat cagcagaaat cagggaaagc ccctaagctc 540

ctgatctatg ctgcatccag tttgcaaagt ggggtcccat caaggttcag tggcagtgga 600

tctgggacag atttcactct caccatcagt agtctgcaac ctgaagattt tgcaacttat 660

tactgtcaac agagttacag tagcccgtgg acattcggcc aagggaccaa ggtggagatc 720

aaaggaggtg gtggatccga tatccagctg acccagtctc cagcttcttt ggctgtgtct 780

ctagggcaga gggccaccat ctcctgcaag gccagccaaa gtgttgatta tgatggtgat 840

agttatttga actggtacca acagattcca ggacagccac ccaaactcct catctatgat 900

gcatccaatc tagtttctgg gatcccaccc aggtttagtg gcagtgggtc tgggacagac 960

ttcaccctca acatccatcc tgtggagaag gtggatgctg caacctatca ctgtcagcaa 1020

agtactgagg atccgtggac gttcggtgga gggaccaagc tcgagatcaa aggtggtggt 1080

ggttctggcg gcggcggctc cggtggtggt ggttctcagg tgcagctgca gcagtctggg 1140

gctgagctgg tgaggcctgg gtcctcagtg aagatttcct gcaaggcttc tggctatgca 1200

ttcagtagct actggatgaa ctgggtgaag cagaggcctg gacagggtct tgagtggatt 1260

ggacagattt ggcctggaga tggtgatact aactacaatg gaaagttcaa gggtaaagcc 1320

actctgactg cagacgaatc ctccagcaca gcctacatgc aactcagcag cctagcatct 1380

gaggactctg cggtctattt ctgtgcaaga cgggagacta cgacggtagg ccgttattac 1440

tatgctatgg actactgggg ccaagggacc acggtcaccg tctcctcc 1488

<210> 210

<211> 496

<212> PRT

<213> artificial sequence

<220>

<223> Human anti-CD3 3-271 VH-VL x anti-CD19 VL-VH

<400> 210

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

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

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

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

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

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

Arg Gly Pro Asp Arg Met Gly His Gly Phe Asp Ile Trp Gly Gln Gly
100 105 110

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

Ser Gly Gly Gly Gly Ser Glu Leu Gln Met Thr Gln Ser Pro Ser Ser
130 135 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145 150 155 160

Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Ser Gly Lys
165 170 175

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
180 185 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
195 200 205

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
210 215 220

Ser Tyr Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
225 230 235 240

Lys Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser
245 250 255

Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser
260 265 270

Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln
275 280 285

Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu
290 295 300

Val Ser Gly Ile Pro Pro Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
305 310 315 320

Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala Thr Tyr
325 330 335

His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr
340 345 350

Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
355 360 365

Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val

370 375 380

Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala
385 390 395 400

Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly
405 410 415

Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr
420 425 430

Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser
435 440 445

Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala
450 455 460

Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr
465 470 475 480

Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
485 490 495

<210> 211

<211> 1494

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 4-10 VH-VL x anti-CD19 VL-VH

<400> 211

gagctgcagc tggtcgagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgggctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct gttagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagccaaa 300

ttcctgggcc actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360

tcaggtggtg gtggttctgg cggcggcggc tccggtggtg gtggttctga gctccagatg 420

acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccgg 480

gcaagtcaga gcattagcag ctatttaaat tggtatcagc agaaaccagg gaaagcccct 540

aagctcctga tctatgctgc atccagtttg caaagtggag tcccatcaag gttcagcggc 600

agtggatctg ggacagagtt cactctcaca atcagcagcc tgcagcctga agattttgca 660

acttattact gtcttcagca taatgcttac ccgtacactt tcggccaggg gaccaaggtg 720

gaaatcaaag gaggtggtgg atccgatatc cagctgaccc agtctccagc ttctttggct 780

gtgtctctag ggcagagggc caccatctcc tgcaaggcca gccaaagtgt tgattatgat 840

ggtgatagtt atttgaactg gtaccaacag attccaggac agccacccaa actcctcatc 900

tatgatgcat ccaatctagt ttctgggatc ccacccaggt ttagtggcag tgggtctggg 960

acagacttca ccctcaacat ccatcctgtg gagaaggtgg atgctgcaac ctatcactgt 1020

cagcaaagta ctgaggatcc gtggacgttc ggtggaggga ccaagctcga gatcaaaggt 1080

ggtggtggtt ctggcggcgg cggctccggt ggtggtggtt ctcaggtgca gctgcagcag 1140

tctggggctg agctggtgag gcctgggtcc tcagtgaaga tttcctgcaa ggcttctggc 1200

tatgcattca gtagctactg gatgaactgg gtgaagcaga ggcctggaca gggtcttgag 1260

tggattggac agatttggcc tggagatggt gatactaact acaatggaaa gttcaagggt 1320

aaagccactc tgactgcaga cgaatcctcc agcacagcct acatgcaact cagcagccta 1380

gcatctgagg actctgcggt ctatttctgt gcaagacggg agactacgac ggtaggccgt 1440

tattactatg ctatggacta ctggggccaa gggaccacgg tcaccgtctc ctcc 1494

<210> 212

<211> 498

<212> PRT

<213> artificial sequence

<220>

<223> Human anti-CD3 4-10 VH-VL x anti-CD19 VL-VH

<400> 212

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

Ser Ala Val Ser Gly Ser Gly Gly Ser Thr 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 Ala Lys Phe Leu Gly His Tyr Tyr Gly Met Asp Val Trp Gly

100 105 110

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

Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Gln Met Thr Gln Ser Pro
130 135 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145 150 155 160

Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro
165 170 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser
180 185 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
195 200 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
210 215 220

Leu Gln His Asn Ala Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val
225 230 235 240

Glu Ile Lys Gly Gly Gly Gly Ser Asp Ile Gln Leu Thr Gln Ser Pro
245 250 255

Ala Ser Leu Ala Val Ser Leu Gly Gln Arg Ala Thr Ile Ser Cys Lys
260 265 270

Ala Ser Gln Ser Val Asp Tyr Asp Gly Asp Ser Tyr Leu Asn Trp Tyr
275 280 285

Gln Gln Ile Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Asp Ala Ser
290 295 300

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

Thr Asp Phe Thr Leu Asn Ile His Pro Val Glu Lys Val Asp Ala Ala
325 330 335

Thr Tyr His Cys Gln Gln Ser Thr Glu Asp Pro Trp Thr Phe Gly Gly
340 345 350

Gly Thr Lys Leu Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly
355 360 365

Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu
370 375 380

Leu Val Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
385 390 395 400

Tyr Ala Phe Ser Ser Tyr Trp Met Asn Trp Val Lys Gln Arg Pro Gly
405 410 415

Gln Gly Leu Glu Trp Ile Gly Gln Ile Trp Pro Gly Asp Gly Asp Thr
420 425 430

Asn Tyr Asn Gly Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Glu
435 440 445

Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Ala Ser Glu Asp
450 455 460

Ser Ala Val Tyr Phe Cys Ala Arg Arg Glu Thr Thr Thr Val Gly Arg
465 470 475 480

Tyr Tyr Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val
485 490 495

Ser Ser

<210> 213

<211> 1518

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 4-48 VH-VL x anti-CD19 VL-VH

<400> 213
gagctgcagc tggtcgagtc tggtcctgtg ctggtgaaac ccacagatac cctcacgctg 60

acttgcaccg tctctgggtt ctcactcaat aatcctagaa tgggtgtgag ctggatccgt 120

cagcccccag ggaagaccct ggagtggctt gcacacattt ttccgagtga cgcaaaagcc 180

cacagtgcat ctctgaagag caggctcacc atctccaagg acacctccaa aagccaggtg 240

gtccctacca tgaccaacat ggaccctgtg gacacagcca catattactg tgcacggata 300

ttgggggaat actatccccc agcctggttc gacccctggg gccagggaac cctggtcacc 360

gtctcctcag gtggtggtgg ttctggcggc ggcggctccg gtggtggtgg ttctgagctc 420

gtgatgacac agtctccaga ctccctggct gtgtctctgg gcgagagggc caccatcaac 480

tgcaagtcca gccagagtgt tttatacagc tccaacaata agaactactt agcttggtac 540

cagcagaaac caggacagcc tcctaagctg ctcatttact gggcatctac ccgggaatcc 600

ggggtccctg accgattcag tggcagcggg tctgggacag atttcactct caccatcagc 660

agcctgcagg ctgaagacgt ggcagtttat tactgtcagc aatatttgaa aatcccttat 720

acttttggcc aggggaccaa ggtggagatc aaaggaggtg gtggatccga tatccagctg 780

acccagtctc cagcttcttt ggctgtgtct ctagggcaga gggccaccat ctcctgcaag 840

gccagccaaa gtgttgatta tgatggtgat agttatttga actggtacca acagattcca 900

ggacagccac ccaaactcct catctatgat gcatccaatc tagtttctgg gatcccaccc 960

aggtttagtg gcagtgggtc tgggacagac ttcaccctca acatccatcc tgtggagaag 1020

gtggatgctg caacctatca ctgtcagcaa agtactgagg atccgtggac gttcggtgga 1080

gggaccaagc tcgagatcaa aggtggtggt ggttctggcg gcggcggctc cggtggtggt 1140

ggttctcagg tgcagctgca gcagtctggg gctgagctgg tgaggcctgg gtcctcagtg 1200

aagatttcct gcaaggcttc tggctatgca ttcagtagct actggatgaa ctgggtgaag 1260

cagaggcctg gacagggtct tgagtggatt ggacagattt ggcctggaga tggtgatact 1320

aactacaatg gaaagttcaa gggtaaagcc actctgactg cagacgaatc ctccagcaca 1380

gcctacatgc aactcagcag cctagcatct gaggactctg cggtctattt ctgtgcaaga 1440

cgggagacta cgacggtagg ccgttattac tatgctatgg actactgggg ccaagggacc 1500

acggtcaccg tctcctcc 1518

<210> 214

<211> 506

<212> PRT

<213> artificial sequence

<220>

<223> Human anti-CD3 4-48 VH-VL x anti-CD19 VL-VH

<400> 214

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

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

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

Trp Leu Ala His Ile Phe Pro Ser Asp Ala Lys Ala His Ser Ala 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 Pro Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

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

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln
130 135 140

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
145 150 155 160

Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
165 170 175

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
180 185 190

Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
195 200 205

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
210 215 220

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Leu Lys Ile Pro Tyr
225 230 235 240

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
245 250 255

Asp Ile Gln Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
260 265 270

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
275 280 285

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
290 295 300

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
305 310 315 320

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
325 330 335

Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
340 345 350

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly

355 360 365

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
370 375 380

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
385 390 395 400

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
405 410 415

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
420 425 430

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
435 440 445

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln
450 455 460

Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
465 470 475 480

Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
485 490 495

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
500 505

<210> 215

<211> 1491

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 3-148 VH-VL

<400> 215

gatatccagc tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttattt gaactggtac 120

caacagattc caggacagcc acccaaactc ctcatctatg atgcatccaa tctagtttct 180

gggatcccac ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggaga aggtggatgc tgcaacctat cactgtcagc aaagtactga ggatccgtgg 300

acgttcggtg gagggaccaa gctcgagatc aaaggtggtg gtggttctgg cggcggcggc 360

tccggtggtg gtggttctca ggtgcagctg cagcagtctg gggctgagct ggtgaggcct 420

gggtcctcag tgaagatttc ctgcaaggct tctggctatg cattcagtag ctactggatg 480

aactgggtga agcagaggcc tggacagggt cttgagtgga ttggacagat ttggcctgga 540

gatggtgata ctaactacaa tggaaagttc aagggtaaag ccactctgac tgcagacgaa 600

tcctccagca cagcctacat gcaactcagc agcctagcat ctgaggactc tgcggtctat 660

ttctgtgcaa gacgggagac tacgacggta ggccgttatt actatgctat ggactactgg 720

ggccaaggga ccacggtcac cgtctcctcc ggaggtggtg gatccgagct gcagctggtc 780

gagtctggcc caggactggt gaagccttcg gggaccctgt ccctcacctg cgctgtctct 840

ggtggctcca tcagcagtag aaactggtgg agttgggtcc gccagccccc agggaagggg 900

ctggagtgga ttggtgatat ctatcatagt gggagcacca actacaaccc gtccctcaag 960

agtcgagtca ccatatcagt agacaagtcc aagaaccagt tctccctgaa gctgagctct 1020

gtgaccgccg cggacacggc cgtgtattac tgtgcgagtg ggtataccag ctgtcgtgat 1080

gcttttgata tctggggcca agggacaatg gtcaccgtct cctcaggtgg tggtggttct 1140

ggcggcggcg gctccggtgg tggtggttct gagctcgtga tgactcagtc tccatcctcc 1200

ctgtctgcat ctgtaggaga cagagtcacc atcacttgcc gggcgagtca gggcattggc 1260

aattatttag cctggtatca gcagaaacca gggcagcctc ctaagatgct catttactgg 1320

gcatcaatcc gggaatccgg ggtccctgac cgattcagtg gcagcgggtc tgggacagac 1380

ttcactctca ccatcagcag cctgcaggct gaagatgtgg cagtttacta ctgtcagcaa 1440

tattatagta atcctcagac gttcggccaa gggaccaagg tggaaatcaa a 1491

<210> 216

<211> 497

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 3-148 VH-VL

<400> 216

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

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

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35 40 45

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

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His

65 70 75 80

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

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
115 120 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130 135 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145 150 155 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
165 170 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180 185 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln
195 200 205

Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
210 215 220

Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
225 230 235 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu
245 250 255

Leu Gln Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly Thr
260 265 270

Leu Ser Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Arg Asn
275 280 285

Trp Trp Ser Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
290 295 300

Gly Asp Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
305 310 315 320

Ser Arg Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser Leu
325 330 335

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
340 345 350

Ser Gly Tyr Thr Ser Cys Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly
355 360 365

Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
370 375 380

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

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
405 410 415

Gln Gly Ile Gly Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
420 425 430

Pro Pro Lys Met Leu Ile Tyr Trp Ala Ser Ile Arg Glu Ser Gly Val
435 440 445

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
450 455 460

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
465 470 475 480

Tyr Tyr Ser Asn Pro Gln Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
485 490 495

Lys

<210> 217

<211> 1509

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 3-190 VH-VL

<400> 217
gatatccagc tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttattt gaactggtac 120

caacagattc caggacagcc acccaaactc ctcatctatg atgcatccaa tctagtttct 180

gggatcccac ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggaga aggtggatgc tgcaacctat cactgtcagc aaagtactga ggatccgtgg 300

acgttcggtg gagggaccaa gctcgagatc aaaggtggtg gtggttctgg cggcggcggc 360

tccggtggtg gtggttctca ggtgcagctg cagcagtctg gggctgagct ggtgaggcct 420

gggtcctcag tgaagatttc ctgcaaggct tctggctatg cattcagtag ctactggatg 480

aactgggtga agcagaggcc tggacagggt cttgagtgga ttggacagat ttggcctgga 540

gatggtgata ctaactacaa tggaaagttc aagggtaaag ccactctgac tgcagacgaa 600

tcctccagca cagcctacat gcaactcagc agcctagcat ctgaggactc tgcggtctat 660

ttctgtgcaa gacgggagac tacgacggta ggccgttatt actatgctat ggactactgg 720

ggccaaggga ccacggtcac cgtctcctcc ggaggtggtg gatccgagct gcagctggtc 780

gagtggggcg caggactgtt gaagccttcg gagaccctgt ccctcacctg cgctgtctat 840

ggtgggtcct tcagtggtta ctactggagc tggatccgcc agcccccagg gaaggggctg 900

gagtggattg gggaaatcaa tcatagtgga agcaccaact acaacccgtc cctcaagagt 960

cgagtcacca tatcagtaga cacgtccaag aaccagttct ccctgaagct gagctctgtg 1020

accgccgcgg acacggctgt gtattactgt gcgagaggcc gaggccgatt tttggggtgg 1080

ttattagggg gctccaactg gttcgacccc tggggccagg gaaccctggt caccgtctcc 1140

tcaggtggtg gtggttctgg cggcggcggc tccggtggtg gtggttctga gctcgtgatg 1200

acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccgg 1260

gcgagtcagg gcattagcaa ttatttaaat tggtatcagc agaaaccagg gaaagcccct 1320

aagctcctga tctacgatgc atccaatttg gaaacagggg tcccatcaag gttcagtggc 1380

agtggatctg ggacagattt cactctcacc atcagcagtc tgcaacctga agattttgca 1440

acttactact gtcaacagag ttacagtacc ccgtacactt ttggccaggg gaccaaagtg 1500

gatatcaaa 1509

<210> 218

<211> 503

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 3-190 VH-VL

<400> 218

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

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

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35 40 45

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

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

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

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
115 120 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130 135 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145 150 155 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
165 170 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180 185 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln
195 200 205

Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
210 215 220

Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
225 230 235 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu
245 250 255

Leu Gln Leu Val Glu Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu Thr
260 265 270

Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr Tyr
275 280 285

Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
290 295 300

Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
305 310 315 320

Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys

325 330 335

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg
340 345 350

Gly Arg Gly Arg Phe Leu Gly Trp Leu Leu Gly Gly Ser Asn Trp Phe
355 360 365

Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
370 375 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met
385 390 395 400

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
405 410 415

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

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser
435 440 445

Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
450 455 460

Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
465 470 475 480

Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr Thr Phe Gly Gln
485 490 495

Gly Thr Lys Val Asp Ile Lys
500

<210> 219

<211> 1488

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 3-271 VH-VL

<400> 219

gatatccagc tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttattt gaactggtac 120

caacagattc caggacagcc acccaaactc ctcatctatg atgcatccaa tctagtttct 180

gggatcccac ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggaga aggtggatgc tgcaacctat cactgtcagc aaagtactga ggatccgtgg 300

acgttcggtg gagggaccaa gctcgagatc aaaggtggtg gtggttctgg cggcggcggc 360

tccggtggtg gtggttctca ggtgcagctg cagcagtctg gggctgagct ggtgaggcct 420

gggtcctcag tgaagatttc ctgcaaggct tctggctatg cattcagtag ctactggatg 480

aactgggtga agcagaggcc tggacagggt cttgagtgga ttggacagat ttggcctgga 540

gatggtgata ctaactacaa tggaaagttc aagggtaaag ccactctgac tgcagacgaa 600

tcctccagca cagcctacat gcaactcagc agcctagcat ctgaggactc tgcggtctat 660

ttctgtgcaa gacgggagac tacgacggta ggccgttatt actatgctat ggactactgg 720

ggccaaggga ccacggtcac cgtctcctcc ggaggtggtg gatccgagct gcagctggtc 780

gagtggggcg caggactgtt gaagccttcg gagaccctgt ccctcacctg cgctgtctat 840

ggtgggtcct tcagtggtta ctactggagc tggatccgcc agcccccagg gaaggggctg 900

gagtggattg gggaaatcaa tcatagtgga agcaccaact acaacccgtc cctcaagagt 960

cgagtcacca tatcagtaga cacgtccaag aaccagttct ccctgaagct gagctctgtg 1020

accgccgcgg acacggctgt gtattactgt gcgagaggcc ctgaccgaat ggggcatggt 1080

tttgatatct ggggccaagg gacaatggtc accgtctcct caggtggtgg tggttctggc 1140

ggcggcggct ccggtggtgg tggttctgag ctccagatga cccagtctcc atcctccctg 1200

tctgcatctg taggagacag agtcaccatc acttgccggg caagtcagag cattagcagc 1260

tatttaaatt ggtatcagca gaaatcaggg aaagccccta agctcctgat ctatgctgca 1320

tccagtttgc aaagtggggt cccatcaagg ttcagtggca gtggatctgg gacagatttc 1380

actctcacca tcagtagtct gcaacctgaa gattttgcaa cttattactg tcaacagagt 1440

tacagtagcc cgtggacatt cggccaaggg accaaggtgg agatcaaa 1488

<210> 220

<211> 496

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 3-271 VH-VL

<400> 220

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

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

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro

35 40 45

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

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

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

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
115 120 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130 135 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145 150 155 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
165 170 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180 185 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln
195 200 205

Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
210 215 220

Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
225 230 235 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu
245 250 255

Leu Gln Leu Val Glu Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu Thr
260 265 270

Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr Tyr
275 280 285

Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly
290 295 300

Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
305 310 315 320

Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys
325 330 335

Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg
340 345 350

Gly Pro Asp Arg Met Gly His Gly Phe Asp Ile Trp Gly Gln Gly Thr
355 360 365

Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
370 375 380

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

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln
405 410 415

Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Ser Gly Lys Ala
420 425 430

Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro
435 440 445

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
450 455 460

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser
465 470 475 480

Tyr Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
485 490 495

<210> 221

<211> 1494

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 4-10 VH-VL

<400> 221

gatatccagc tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttattt gaactggtac 120

caacagattc caggacagcc acccaaactc ctcatctatg atgcatccaa tctagtttct 180

gggatcccac ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240

cctgtggaga aggtggatgc tgcaacctat cactgtcagc aaagtactga ggatccgtgg 300

acgttcggtg gagggaccaa gctcgagatc aaaggtggtg gtggttctgg cggcggcggc 360

tccggtggtg gtggttctca ggtgcagctg cagcagtctg gggctgagct ggtgaggcct 420

gggtcctcag tgaagatttc ctgcaaggct tctggctatg cattcagtag ctactggatg 480

aactgggtga agcagaggcc tggacagggt cttgagtgga ttggacagat ttggcctgga 540

gatggtgata ctaactacaa tggaaagttc aagggtaaag ccactctgac tgcagacgaa 600

tcctccagca cagcctacat gcaactcagc agcctagcat ctgaggactc tgcggtctat 660

ttctgtgcaa gacgggagac tacgacggta ggccgttatt actatgctat ggactactgg 720

ggccaaggga ccacggtcac cgtctcctcc ggaggtggtg gatccgagct gcagctggtc 780

gagtctgggg gaggcttggt acagcctggg gggtccctga gactctcctg tgcagcctct 840

ggattcacct ttagcagcta tgccatgggc tgggtccgcc aggctccagg gaaggggctg 900

gagtgggtct cagctgttag tggtagtggt ggtagcacat actacgcaga ctccgtgaag 960

ggccggttca ccatctccag agacaattcc aagaacacgc tgtatctgca aatgaacagc 1020

ctgagagccg aggacacggc cgtatattac tgtgcgaaag ccaaattcct gggccactac 1080

tacggtatgg acgtctgggg ccaagggacc acggtcaccg tctcctcagg tggtggtggt 1140

tctggcggcg gcggctccgg tggtggtggt tctgagctcc agatgaccca gtctccatcc 1200

tccctgtctg catctgtagg agacagagtc accatcactt gccgggcaag tcagagcatt 1260

agcagctatt taaattggta tcagcagaaa ccagggaaag cccctaagct cctgatctat 1320

gctgcatcca gtttgcaaag tggagtccca tcaaggttca gcggcagtgg atctgggaca 1380

gagttcactc tcacaatcag cagcctgcag cctgaagatt ttgcaactta ttactgtctt 1440

cagcataatg cttacccgta cactttcggc caggggacca aggtggaaat caaa 1494

<210> 222

<211> 498

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 4-10 VH-VL

<400> 222

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

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

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35 40 45

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

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

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

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
            100                 105                 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
        115                 120                 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
    130                 135                 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145                 150                 155                 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
                165                 170                 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
            180                 185                 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln
        195                 200                 205

Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
    210                 215                 220

Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
225                 230                 235                 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu
                245                 250                 255

Leu Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser
            260                 265                 270

Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala
        275                 280                 285

Met Gly Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser
    290                 295                 300

Ala Val Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
305                 310                 315                 320
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Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
325 330 335

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
340 345 350

Lys Ala Lys Phe Leu Gly His Tyr Tyr Gly Met Asp Val Trp Gly Gln
355 360 365

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
370 375 380

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

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
405 410 415

Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
420 425 430

Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly
435 440 445

Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu
450 455 460

Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu
465 470 475 480

Gln His Asn Ala Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu
485 490 495

Ile Lys

<210> 223

<211> 1518

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD19 VL-VH x human anti-CD3 4-48 VH-VL

<400> 223
gatatccagc tgacccagtc tccagcttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca aggccagcca aagtgttgat tatgatggtg atagttattt gaactggtac 120

caacagattc caggacagcc acccaaactc ctcatctatg atgcatccaa tctagtttct 180

gggatcccac ccaggtttag tggcagtggg tctgggacag acttcaccct caacatccat 240
cctgtggaga aggtggatgc tgcaacctat cactgtcagc aaagtactga ggatccgtgg 300
acgttcggtg gagggaccaa gctcgagatc aaaggtggtg gtggttctgg cggcggcggc 360
tccggtggtg gtggttctca ggtgcagctg cagcagtctg gggctgagct ggtgaggcct 420
gggtcctcag tgaagatttc ctgcaaggct tctggctatg cattcagtag ctactggatg 480
aactgggtga agcagaggcc tggacagggt cttgagtgga ttggacagat ttggcctgga 540
gatggtgata ctaactacaa tggaaagttc aagggtaaag ccactctgac tgcagacgaa 600
tcctccagca cagcctacat gcaactcagc agcctagcat ctgaggactc tgcggtctat 660
ttctgtgcaa gacgggagac tacgacggta ggccgttatt actatgctat ggactactgg 720
ggccaaggga ccacggtcac cgtctcctcc ggaggtggtg gatccgagct gcagctggtc 780
gagtctggtc ctgtgctggt gaaacccaca gataccctca cgctgacttg caccgtctct 840
gggttctcac tcaataatcc tagaatgggt gtgagctgga tccgtcagcc cccagggaag 900
accctggagt ggcttgcaca catttttccg agtgacgcaa aagcccacag tgcatctctg 960
aagagcaggc tcaccatctc caaggacacc tccaaaagcc aggtggtccc taccatgacc 1020
aacatggacc ctgtggacac agccacatat tactgtgcac ggatattggg ggaatactat 1080
cccccagcct ggttcgaccc ctggggccag ggaaccctgg tcaccgtctc ctcaggtggt 1140
ggtggttctg gcggcggcgg ctccggtggt ggtggttctg agctcgtgat gacacagtct 1200
ccagactccc tggctgtgtc tctgggcgag agggccacca tcaactgcaa gtccagccag 1260
agtgttttat acagctccaa caataagaac tacttagctt ggtaccagca gaaaccagga 1320
cagcctccta agctgctcat ttactgggca tctacccggg aatccggggt ccctgaccga 1380
ttcagtggca gcgggtctgg gacagatttc actctcacca tcagcagcct gcaggctgaa 1440
gacgtggcag tttattactg tcagcaatat ttgaaaatcc cttatacttt tggccagggg 1500
accaaggtgg agatcaaa 1518

<210> 224
<211> 506
<212> PRT
<213> artificial sequence

<220>
<223> anti-CD19 VL-VH x human anti-CD3 4-48 VH-VL

<400> 224

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

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp

20 25 30

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35 40 45

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

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

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

Glu Asp Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val
115 120 125

Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser Ser Val
130 135 140

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr Trp Met
145 150 155 160

Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly Gln
165 170 175

Ile Trp Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe Lys Gly
180 185 190

Lys Ala Thr Leu Thr Ala Asp Glu Ser Ser Ser Thr Ala Tyr Met Gln
195 200 205

Leu Ser Ser Leu Ala Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
210 215 220

Arg Glu Thr Thr Thr Val Gly Arg Tyr Tyr Tyr Ala Met Asp Tyr Trp
225 230 235 240

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu
245 250 255

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

Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Asn Asn Pro Arg
275 280 285

Met Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Thr Leu Glu Trp
290 295 300

Leu Ala His Ile Phe Pro Ser Asp Ala Lys Ala His Ser Ala Ser Leu
305 310 315 320

Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Ser Gln Val Val
325 330 335

Pro Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys
340 345 350

Ala Arg Ile Leu Gly Glu Tyr Tyr Pro Pro Ala Trp Phe Asp Pro Trp
355 360 365

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
370 375 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser
385 390 395 400

Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys
405 410 415

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
420 425 430

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr
435 440 445

Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
450 455 460

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu
465 470 475 480

Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Leu Lys Ile Pro Tyr Thr
485 490 495

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
500 505

<210> 225

<211> 1485

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 3-148 VH-VL x anti-EpCAM 5-10 VH-VL

<400> 225

gagctgcagc tggtcgagtc tggcccagga ctggtgaagc cttcggggac cctgtccctc 60

acctgcgctg tctctggtgg ctccatcagc agtagaaact ggtggagttg ggtccgccag 120

cccccaggga aggggctgga gtggattggt gatatctatc atagtgggag caccaactac 180

aacccgtccc tcaagagtcg agtcaccata tcagtagaca agtccaagaa ccagttctcc 240

ctgaagctga gctctgtgac cgccgcggac acggccgtgt attactgtgc gagtgggtat 300

accagctgtc gtgatgcttt tgatatctgg ggccaaggga caatggtcac cgtctcctca 360

ggtggtggtg gttctggcgg cggcggctcc ggtggtggtg gttctgagct cgtgatgact 420

cagtctccat cctccctgtc tgcatctgta ggagacagag tcaccatcac ttgccgggcg 480

agtcagggca ttggcaatta tttagcctgg tatcagcaga aaccagggca gcctcctaag 540

atgctcattt actgggcatc aatccgggaa tccggggtcc ctgaccgatt cagtggcagc 600

gggtctggga cagacttcac tctcaccatc agcagcctgc aggctgaaga tgtggcagtt 660

tactactgtc agcaatatta tagtaatcct cagacgttcg gccaagggac caaggtggaa 720

atcaaaggag gtggtggatc cgaggtgcag ctgctcgagc agtctggagc tgagctggta 780

aggcctggga cttcagtgaa gatatcctgc aaggcttctg gatacgcctt cactaactac 840

tggctaggtt gggtaaagca gaggcctgga catggacttg agtggattgg agatattttc 900

cctggaagtg gtaatatcca ctacaatgag aagttcaagg gcaaagccac actgactgca 960

gacaaatctt cgagcacagc ctatatgcag ctcagtagcc tgacatttga ggactctgct 1020

gtctatttct gtgcaagact gaggaactgg gacgagccta tggactactg gggccaaggg 1080

accacggtca ccgtctcctc aggtggtggt ggttctggcg gcggcggctc cggtggtggt 1140

ggttctgagc tcgtgatgac acagtctcca tcctccctga ctgtgacagc aggagagaag 1200

gtcactatga gctgcaagtc cagtcagagt ctgttaaaca gtggaaatca aaagaactac 1260

ttgacctggt accagcagaa accagggcag cctcctaaac tgttgatcta ctgggcatcc 1320

actagggaat ctggggtccc tgatcgcttc acaggcagtg gatctggaac agatttcact 1380

ctcaccatca gcagtgtgca ggctgaagac ctggcagttt attactgtca gaatgattat 1440

agttatccgc tcacgttcgg tgctgggacc aagcttgaga tcaaa 1485

<210> 226

<211> 495

<212> PRT

<213> artificial sequence

<220>

<223> Human anti-CD3 3-148 VH-VL x anti-EpCAM 5-10 VH-VL

<400> 226

Glu Leu Gln Leu Val 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 Ser Ser Arg
            20                  25                  30

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

Ile Gly Asp Ile Tyr His Ser 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 Gln 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 Ser Gly Tyr Thr Ser Cys Arg Asp Ala Phe Asp Ile Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln Ser Pro Ser
    130                 135                 140

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala
145                 150                 155                 160

Ser Gln Gly Ile Gly Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly
                165                 170                 175

Gln Pro Pro Lys Met Leu Ile Tyr Trp Ala Ser Ile Arg Glu Ser Gly
            180                 185                 190

Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu
        195                 200                 205

Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln
    210                 215                 220

Gln Tyr Tyr Ser Asn Pro Gln Thr Phe Gly Gln Gly Thr Lys Val Glu
225                 230                 235                 240

Ile Lys Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser Gly
                245                 250                 255

Ala Glu Leu Val Arg Pro Gly Thr Ser Val Lys Ile Ser Cys Lys Ala
            260                 265                 270

Ser Gly Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys Gln Arg
        275                 280                 285
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Pro Gly His Gly Leu Glu Trp Ile Gly Asp Ile Phe Pro Gly Ser Gly
290 295 300

Asn Ile His Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala
305 310 315 320

Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Phe
325 330 335

Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp Asp Glu
340 345 350

Pro Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly
355 360 365

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu
370 375 380

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

Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn
405 410 415

Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
420 425 430

Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp
435 440 445

Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
450 455 460

Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn Asp Tyr
465 470 475 480

Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys
485 490 495

<210> 227

<211> 1503

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 3-190 VH-VL x anti- EpCAM 5-10 VH-VL

<400> 227
gagctgcagc tggtcgagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120
ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240
aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggccgaggc 300
cgatttttgg ggtggttatt aggggctcc aactggttcg acccctgggg ccagggaacc 360
ctggtcaccg tctcctcagg tggtggtggt tctggcggcg gcggctccgg tggtggtggt 420
tctgagctcg tgatgaccca gtctccatcc tccctgtctg catctgtagg agacagagtc 480
accatcactt gccgggcgag tcagggcatt agcaattatt taaattggta tcagcagaaa 540
ccagggaaag cccctaagct cctgatctac gatgcatcca atttggaaac aggggtccca 600
tcaaggttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagtctgcaa 660
cctgaagatt ttgcaactta ctactgtcaa cagagttaca gtaccccgta cacttttggc 720
caggggacca aagtggatat caaaggaggt ggtggatccg aggtgcagct gctcgagcag 780
tctggagctg agctggtaag gcctgggact tcagtgaaga tatcctgcaa ggcttctgga 840
tacgccttca ctaactactg gctaggttgg gtaaagcaga ggcctggaca tggacttgag 900
tggattggag atattttccc tggaagtggt aatatccact acaatgagaa gttcaagggc 960
aaagccacac tgactgcaga caaatcttcg agcacagcct atatgcagct cagtagcctg 1020
acatttgagg actctgctgt ctatttctgt gcaagactga ggaactggga cgagcctatg 1080
gactactggg gccaagggac cacggtcacc gtctcctcag gtggtggtgg ttctggcggc 1140
ggcggctccg gtggtggtgg ttctgagctc gtgatgacac agtctccatc ctccctgact 1200
gtgacagcag gagagaaggt cactatgagc tgcaagtcca gtcagagtct gttaaacagt 1260
ggaaatcaaa agaactactt gacctggtac cagcagaaac cagggcagcc tcctaaactg 1320
ttgatctact gggcatccac tagggaatct ggggtccctg atcgcttcac aggcagtgga 1380
tctggaacag atttcactct caccatcagc agtgtgcagg ctgaagacct ggcagtttat 1440
tactgtcaga atgattatag ttatccgctc acgttcggtg ctgggaccaa gcttgagatc 1500
aaa 1503

<210> 228
<211> 501
<212> PRT
<213> artificial sequence

<220>
<223> Human anti-CD3 3-190 VH-VL x anti- EpCAM 5-10 VH-VL
<400> 228
Glu Leu Gln Leu Val Glu Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu

1 5 10 15

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

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

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

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

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

Arg Gly Arg Gly Arg Phe Leu Gly Trp Leu Leu Gly Gly Ser Asn Trp
100 105 110

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

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val
130 135 140

Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val
145 150 155 160

Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Asn Trp
165 170 175

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala
180 185 190

Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
195 200 205

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
210 215 220

Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr Thr Phe Gly
225 230 235 240

Gln Gly Thr Lys Val Asp Ile Lys Gly Gly Gly Gly Ser Glu Val Gln
245 250 255

Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Thr Ser Val
260 265 270

Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Trp Leu
275 280 285

Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp Ile Gly Asp
290 295 300

Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys Phe Lys Gly
305 310 315 320

Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
325 330 335

Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg
340 345 350

Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln Gly Thr Thr
355 360 365

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
370 375 380

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

Val Thr Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser
405 410 415

Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln
420 425 430

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg
435 440 445

Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp
450 455 460

Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr
465 470 475 480

Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr
485 490 495

Lys Leu Glu Ile Lys
500

<210> 229

<211> 1482

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 3-271 VH-VL x anti- EpCAM 5-10 VH-VL

<400> 229

gagctgcagc tggtcgagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac 180

ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggccctgac 300

cgaatggggc atggttttga tatctggggc caagggacaa tggtcaccgt ctcctcaggt 360

ggtggtggtt ctggcggcgg cggctccggt ggtggtggtt ctgagctcca gatgacccag 420

tctccatcct ccctgtctgc atctgtagga gacagagtca ccatcacttg ccgggcaagt 480

cagagcatta gcagctattt aaattggtat cagcagaaat cagggaaagc ccctaagctc 540

ctgatctatg ctgcatccag tttgcaaagt ggggtcccat caaggttcag tggcagtgga 600

tctgggacag atttcactct caccatcagt agtctgcaac ctgaagattt tgcaacttat 660

tactgtcaac agagttacag tagcccgtgg acattcggcc aagggaccaa ggtggagatc 720

aaaggaggtg gtggatccga ggtgcagctg ctcgagcagt ctggagctga gctggtaagg 780

cctgggactt cagtgaagat atcctgcaag gcttctggat acgccttcac taactactgg 840

ctaggttggg taaagcagag gcctggacat ggacttgagt ggattggaga tattttccct 900

ggaagtggta atatccacta caatgagaag ttcaagggca aagccacact gactgcagac 960

aaatcttcga gcacagccta tatgcagctc agtagcctga catttgagga ctctgctgtc 1020

tatttctgtg caagactgag gaactgggac gagcctatgg actactgggg ccaagggacc 1080

acggtcaccg tctcctcagg tggtggtggt tctggcggcg gcggctccgg tggtggtggt 1140

tctgagctcg tgatgacaca gtctccatcc tccctgactg tgacagcagg agagaaggtc 1200

actatgagct gcaagtccag tcagagtctg ttaaacagtg gaaatcaaaa gaactacttg 1260

acctggtacc agcagaaacc agggcagcct cctaaactgt tgatctactg ggcatccact 1320

agggaatctg gggtccctga tcgcttcaca ggcagtggat ctggaacaga tttcactctc 1380

accatcagca gtgtgcaggc tgaagacctg gcagtttatt actgtcagaa tgattatagt 1440

tatccgctca cgttcggtgc tgggaccaag cttgagatca aa 1482

<210> 230

<211> 494

<212> PRT

<213> artificial sequence

<220>

<223> Human anti-CD3 3-271 VH-VL x anti- EpCAM 5-10 VH-VL

<400> 230

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

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

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

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

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

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

Arg Gly Pro Asp Arg Met Gly His Gly Phe Asp Ile Trp Gly Gln Gly
            100                 105                 110

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

Ser Gly Gly Gly Gly Ser Glu Leu Gln Met Thr Gln Ser Pro Ser Ser
    130                 135                 140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145                 150                 155                 160

Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Ser Gly Lys
                165                 170                 175

Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
            180                 185                 190

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        195                 200                 205

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    210                 215                 220

Ser Tyr Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
225                 230                 235                 240

Lys Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser Gly Ala
                245                 250                 255

Glu Leu Val Arg Pro Gly Thr Ser Val Lys Ile Ser Cys Lys Ala Ser
            260                 265                 270
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Gly Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro
275 280 285

Gly His Gly Leu Glu Trp Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn
290 295 300

Ile His Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp
305 310 315 320

Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu
325 330 335

Asp Ser Ala Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro
340 345 350

Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly
355 360 365

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val
370 375 380

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

Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln
405 410 415

Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys
420 425 430

Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg
435 440 445

Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
450 455 460

Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser
465 470 475 480

Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys
485 490

<210> 231

<211> 1488

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 4-10 VH-VL x anti- EpCAM 5-10 VH-VL

<400> 231

gagctgcagc tggtcgagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttagc agctatgcca tgggctgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcagct gttagtggta gtggtggtag cacatactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgc gaaagccaaa 300

ttcctgggcc actactacgg tatggacgtc tggggccaag ggaccacggt caccgtctcc 360

tcaggtggtg gtggttctgg cggcggcggc tccggtggtg gtggttctga gctccagatg 420

acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccgg 480

gcaagtcaga gcattagcag ctatttaaat tggtatcagc agaaaccagg gaaagcccct 540

aagctcctga tctatgctgc atccagtttg caaagtggag tcccatcaag gttcagcggc 600

agtggatctg ggacagagtt cactctcaca atcagcagcc tgcagcctga agattttgca 660

acttattact gtcttcagca taatgcttac ccgtacactt tcggccaggg gaccaaggtg 720

gaaatcaaag gaggtggtgg atccgaggtg cagctgctcg agcagtctgg agctgagctg 780

gtaaggcctg ggacttcagt gaagatatcc tgcaaggctt ctggatacgc cttcactaac 840

tactggctag gttgggtaaa gcagaggcct ggacatggac ttgagtggat tggagatatt 900

ttccctggaa gtggtaatat ccactacaat gagaagttca agggcaaagc cacactgact 960

gcagacaaat cttcgagcac agcctatatg cagctcagta gcctgacatt tgaggactct 1020

gctgtctatt tctgtgcaag actgaggaac tgggacgagc ctatggacta ctggggccaa 1080

gggaccacgg tcaccgtctc ctcaggtggt ggtggttctg gcggcggcgg ctccggtggt 1140

ggtggttctg agctcgtgat gacacagtct ccatcctccc tgactgtgac agcaggagag 1200

aaggtcacta tgagctgcaa gtccagtcag agtctgttaa acagtggaaa tcaaaagaac 1260

tacttgacct ggtaccagca gaaaccaggg cagcctccta aactgttgat ctactgggca 1320

tccactaggg aatctggggt ccctgatcgc ttcacaggca gtggatctgg aacagatttc 1380

actctcacca tcagcagtgt gcaggctgaa gacctggcag tttattactg tcagaatgat 1440

tatagttatc cgctcacgtt cggtgctggg accaagcttg agatcaaa 1488

<210> 232

<211> 496

<212> PRT

<213> artificial sequence

<220>

<223> Human anti-CD3 4-10 VH-VL x anti- EpCAM 5-10 VH-VL

<400> 232

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

Ser Ala Val Ser Gly Ser Gly Gly Ser Thr 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 Ala Lys Phe Leu Gly His Tyr Tyr Gly Met Asp Val Trp Gly
            100                 105                 110

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

Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Gln Met Thr Gln Ser Pro
    130                 135                 140

Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg
145                 150                 155                 160

Ala Ser Gln Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro
                165                 170                 175

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser
            180                 185                 190

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr
        195                 200                 205

Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
    210                 215                 220

Leu Gln His Asn Ala Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val
225                 230                 235                 240

Glu Ile Lys Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser
                245                 250                 255

Gly Ala Glu Leu Val Arg Pro Gly Thr Ser Val Lys Ile Ser Cys Lys
            260                 265                 270
```

Ala Ser Gly Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys Gln
275 280 285

Arg Pro Gly His Gly Leu Glu Trp Ile Gly Asp Ile Phe Pro Gly Ser
290 295 300

Gly Asn Ile His Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr
305 310 315 320

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
325 330 335

Phe Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp Asp
340 345 350

Glu Pro Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
355 360 365

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
370 375 380

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

Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly
405 410 415

Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln Pro
420 425 430

Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro
435 440 445

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
450 455 460

Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn Asp
465 470 475 480

Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile Lys
485 490 495

<210> 233

<211> 1512

<212> DNA

<213> artificial sequence

<220>

<223> Human anti-CD3 4-48 VH-VL x anti- EpCAM 5-10 VH-VL

<400> 233
gagctgcagc tggtcgagtc tggtcctgtg ctggtgaaac ccacagatac cctcacgctg 60
acttgcaccg tctctgggtt ctcactcaat aatcctagaa tgggtgtgag ctggatccgt 120
cagcccccag ggaagaccct ggagtggctt gcacacattt ttccgagtga cgcaaaagcc 180
cacagtgcat ctctgaagag caggctcacc atctccaagg acacctccaa aagccaggtg 240
gtccctacca tgaccaacat ggaccctgtg gacacagcca catattactg tgcacggata 300
ttgggggaat actatccccc agcctggttc gacccctggg gccagggaac cctggtcacc 360
gtctcctcag gtggtggtgg ttctggcggc ggcggctccg gtggtggtgg ttctgagctc 420
gtgatgacac agtctccaga ctccctggct gtgtctctgg gcgagagggc caccatcaac 480
tgcaagtcca gccagagtgt tttatacagc tccaacaata agaactactt agcttggtac 540
cagcagaaac caggacagcc tcctaagctg ctcatttact gggcatctac ccgggaatcc 600
ggggtccctg accgattcag tggcagcggg tctgggacag atttcactct caccatcagc 660
agcctgcagg ctgaagacgt ggcagtttat tactgtcagc aatatttgaa aatcccttat 720
acttttggcc aggggaccaa ggtggagatc aaaggaggtg gtggatccga ggtgcagctg 780
ctcgagcagt ctggagctga gctggtaagg cctgggactt cagtgaagat atcctgcaag 840
gcttctggat acgccttcac taactactgg ctaggttggg taaagcagag gcctggacat 900
ggacttgagt ggattggaga tattttccct ggaagtggta atatccacta caatgagaag 960
ttcaagggca aagccacact gactgcagac aaatcttcga gcacagccta tatgcagctc 1020
agtagcctga catttgagga ctctgctgtc tatttctgtg caagactgag gaactgggac 1080
gagcctatgg actactgggg ccaagggacc acggtcaccg tctcctcagg tggtggtggt 1140
tctggcggcg gcggctccgg tggtggtggt tctgagctcg tgatgacaca gtctccatcc 1200
tccctgactg tgacagcagg agagaaggtc actatgagct gcaagtccag tcagagtctg 1260
ttaaacagtg gaaatcaaaa gaactacttg acctggtacc agcagaaacc agggcagcct 1320
cctaaactgt tgatctactg ggcatccact agggaatctg gggtccctga tcgcttcaca 1380
ggcagtggat ctggaacaga tttcactctc accatcagca gtgtgcaggc tgaagacctg 1440
gcagtttatt actgtcagaa tgattatagt tatccgctca cgttcggtgc tgggaccaag 1500
cttgagatca aa 1512

<210> 234
<211> 504
<212> PRT
<213> artificial sequence

<220>
<223> Human anti-CD3 4-48 VH-VL x anti- EpCAM 5-10 VH-VL

<400> 234

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

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

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

Trp Leu Ala His Ile Phe Pro Ser Asp Ala Lys Ala His Ser Ala 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 Pro Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

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

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

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln
130 135 140

Ser Pro Asp Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn
145 150 155 160

Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr
165 170 175

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile
180 185 190

Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
195 200 205

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
210 215 220

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Leu Lys Ile Pro Tyr
225 230 235 240

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
245 250 255

Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
260 265 270

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
275 280 285

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
290 295 300

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
305 310 315 320

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
325 330 335

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
340 345 350

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
355 360 365

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
370 375 380

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

Ser Leu Thr Val Thr Ala Gly Glu Lys Val Thr Met Ser Cys Lys Ser
405 410 415

Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu Thr Trp
420 425 430

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala
435 440 445

Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser
450 455 460

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Leu
465 470 475 480

Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser Tyr Pro Leu Thr Phe Gly
485 490 495

Ala Gly Thr Lys Leu Glu Ile Lys
500

<210> 235

<211> 1485

<212> DNA

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 3-148 VH-VL

<400> 235

gagctcgtga tgacacagtc tccatcctcc ctgactgtga cagcaggaga gaaggtcact 60

atgagctgca agtccagtca gagtctgtta aacagtggaa atcaaaagaa ctacttgacc 120

tggtaccagc agaaaccagg gcagcctcct aaactgttga tctactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240

atcagcagtg tgcaggctga agacctggca gtttattact gtcagaatga ttatagttat 300

ccgctcacgt tcggtgctgg gaccaagctt gagatcaaag gtggtggtgg ttctggcggc 360

ggcggctccg gtggtggtgg ttctgaggtg cagctgctcg agcagtctgg agctgagctg 420

gtaaggcctg ggacttcagt gaagatatcc tgcaaggctt ctggatacgc cttcactaac 480

tactggctag gttgggtaaa gcagaggcct ggacatggac ttgagtggat tggagatatt 540

ttccctggaa gtggtaatat ccactacaat gagaagttca agggcaaagc cacactgact 600

gcagacaaat cttcgagcac agcctatatg cagctcagta gcctgacatt tgaggactct 660

gctgtctatt tctgtgcaag actgaggaac tgggacgagc ctatggacta ctggggccaa 720

gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg agctgcagct ggtcgagtct 780

ggcccaggac tggtgaagcc ttcggggacc ctgtccctca cctgcgctgt ctctggtggc 840

tccatcagca gtagaaactg gtggagttgg gtccgccagc ccccagggaa ggggctggag 900

tggattggtg atatctatca tagtgggagc accaactaca acccgtccct caagagtcga 960

gtcaccatat cagtagacaa gtccaagaac cagttctccc tgaagctgag ctctgtgacc 1020

gccgcggaca cggccgtgta ttactgtgcg agtgggtata ccagctgtcg tgatgctttt 1080

gatatctggg gccaagggac aatggtcacc gtctcctcag gtggtggtgg ttctggcggc 1140

ggcggctccg gtggtggtgg ttctgagctc gtgatgactc agtctccatc ctccctgtct 1200

gcatctgtag gagacagagt caccatcact tgccgggcga gtcagggcat tggcaattat 1260

ttagcctggt atcagcagaa accagggcag cctcctaaga tgctcattta ctgggcatca 1320

atccgggaat ccggggtccc tgaccgattc agtggcagcg ggtctgggac agacttcact 1380

ctcaccatca gcagcctgca ggctgaagat gtggcagttt actactgtca gcaatattat 1440

agtaatcctc agacgttcgg ccaagggacc aaggtggaaa tcaaa 1485

<210> 236

<211> 495

<212> PRT

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 3-148 VH-VL

<400> 236

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
100 105 110

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
130 135 140

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
145 150 155 160

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
165 170 175

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
180 185 190

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
195 200 205

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
210 215 220

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
225 230 235 240

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Gln
245 250 255

Leu Val Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gly Thr Leu Ser
260 265 270

Leu Thr Cys Ala Val Ser Gly Gly Ser Ile Ser Ser Arg Asn Trp Trp
275 280 285

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

Ile Tyr His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg
305 310 315 320

Val Thr Ile Ser Val Asp Lys Ser Lys Asn Gln Phe Ser Leu Lys Leu
325 330 335

Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Ser Gly
340 345 350

Tyr Thr Ser Cys Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
355 360 365

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
370 375 380

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

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly
405 410 415

Ile Gly Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
420 425 430

Lys Met Leu Ile Tyr Trp Ala Ser Ile Arg Glu Ser Gly Val Pro Asp
435 440 445

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
450 455 460

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr
465 470 475 480

Ser Asn Pro Gln Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
485 490 495

<210> 237

<211> 1503

<212> DNA

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 3-190 VH-VL

<400> 237

gagctcgtga tgacacagtc tccatcctcc ctgactgtga cagcaggaga gaaggtcact 60

atgagctgca agtccagtca gagtctgtta aacagtggaa atcaaaagaa ctacttgacc 120

tggtaccagc agaaaccagg gcagcctcct aaactgttga tctactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240

atcagcagtg tgcaggctga agacctggca gtttattact gtcagaatga ttatagttat 300

ccgctcacgt tcggtgctgg gaccaagctt gagatcaaag gtggtggtgg ttctggcggc 360

ggcggctccg gtggtggtgg ttctgaggtg cagctgctcg agcagtctgg agctgagctg 420

gtaaggcctg ggacttcagt gaagatatcc tgcaaggctt ctggatacgc cttcactaac 480

tactggctag gttgggtaaa gcagaggcct ggacatggac ttgagtggat tggagatatt 540

ttccctggaa gtggtaatat ccactacaat gagaagttca agggcaaagc cacactgact 600

gcagacaaat cttcgagcac agcctatatg cagctcagta gcctgacatt tgaggactct 660

gctgtctatt tctgtgcaag actgaggaac tgggacgagc ctatggacta ctggggccaa 720

gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg agctgcagct ggtcgagtgg 780

ggcgcaggac tgttgaagcc ttcggagacc ctgtccctca cctgcgctgt ctatggtggg 840

tccttcagtg gttactactg gagctggatc cgccagcccc cagggaaggg gctggagtgg 900

attggggaaa tcaatcatag tggaagcacc aactacaacc cgtccctcaa gagtcgagtc 960

accatatcag tagacacgtc caagaaccag ttctccctga agctgagctc tgtgaccgcc 1020

gcggacacgg ctgtgtatta ctgtgcgaga ggccgaggcc gatttttggg gtggttatta 1080

gggggctcca actggttcga cccctggggc cagggaaccc tggtcaccgt ctcctcaggt 1140

ggtggtggtt ctggcggcgg cggctccggt ggtggtggtt ctgagctcgt gatgacccag 1200

tctccatcct ccctgtctgc atctgtagga gacagagtca ccatcacttg ccgggcgagt 1260

cagggcatta gcaattattt aaattggtat cagcagaaac cagggaaagc ccctaagctc 1320

ctgatctacg atgcatccaa tttggaaaca ggggtcccat caaggttcag tggcagtgga 1380

tctgggacag atttcactct caccatcagc agtctgcaac ctgaagattt tgcaacttac 1440

tactgtcaac agagttacag taccccgtac acttttggcc aggggaccaa agtggatatc 1500

aaa 1503

<210> 238

<211> 501

<212> PRT

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 3-190 VH-VL

<400> 238

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

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

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
    130                 135                 140

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
145                 150                 155                 160

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
                165                 170                 175

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
            180                 185                 190

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
        195                 200                 205

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
    210                 215                 220

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
225                 230                 235                 240

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Gln
                245                 250                 255
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Leu Val Glu Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu Thr Leu Ser
260 265 270

Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
275 280 285

Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile
290 295 300

Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val
305 310 315 320

Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser
325 330 335

Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg
340 345 350

Gly Arg Phe Leu Gly Trp Leu Leu Gly Gly Ser Asn Trp Phe Asp Pro
355 360 365

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
370 375 380

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met Thr Gln
385 390 395 400

Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr
405 410 415

Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln
420 425 430

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu
435 440 445

Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
450 455 460

Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
465 470 475 480

Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr
485 490 495

Lys Val Asp Ile Lys
500

<210> 239

<211> 1482

<212> DNA

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 3-271 VH-VL

<400> 239

gagctcgtga tgacacagtc tccatcctcc ctgactgtga cagcaggaga gaaggtcact 60

atgagctgca agtccagtca gagtctgtta aacagtggaa atcaaaagaa ctacttgacc 120

tggtaccagc agaaaccagg gcagcctcct aaactgttga tctactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240

atcagcagtg tgcaggctga agacctggca gtttattact gtcagaatga ttatagttat 300

ccgctcacgt tcggtgctgg gaccaagctt gagatcaaag gtggtggtgg ttctggcggc 360

ggcggctccg gtggtggtgg ttctgaggtg cagctgctcg agcagtctgg agctgagctg 420

gtaaggcctg ggacttcagt gaagatatcc tgcaaggctt ctggatacgc cttcactaac 480

tactggctag gttgggtaaa gcagaggcct ggacatggac ttgagtggat tggagatatt 540

ttccctggaa gtggtaatat ccactacaat gagaagttca agggcaaagc cacactgact 600

gcagacaaat cttcgagcac agcctatatg cagctcagta gcctgacatt tgaggactct 660

gctgtctatt tctgtgcaag actgaggaac tgggacgagc ctatggacta ctggggccaa 720

gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg agctgcagct ggtcgagtgg 780

ggcgcaggac tgttgaagcc ttcggagacc ctgtccctca cctgcgctgt ctatggtggg 840

tccttcagtg gttactactg gagctggatc cgccagcccc cagggaaggg gctggagtgg 900

attggggaaa tcaatcatag tggaagcacc aactacaacc cgtccctcaa gagtcgagtc 960

accatatcag tagacacgtc caagaaccag ttctccctga agctgagctc tgtgaccgcc 1020

gcggacacgg ctgtgtatta ctgtgcgaga ggccctgacc gaatggggca tggttttgat 1080

atctggggcc aagggacaat ggtcaccgtc tcctcaggtg gtggtggttc tggcggcggc 1140

ggctccggtg gtggtggttc tgagctccag atgacccagt ctccatcctc cctgtctgca 1200

tctgtaggag acagagtcac catcacttgc cgggcaagtc agagcattag cagctattta 1260

aattggtatc agcagaaatc agggaaagcc cctaagctcc tgatctatgc tgcatccagt 1320

ttgcaaagtg gggtcccatc aaggttcagt ggcagtggat ctgggacaga tttcactctc 1380

accatcagta gtctgcaacc tgaagatttt gcaacttatt actgtcaaca gagttacagt 1440

agcccgtgga cattcggcca agggaccaag gtggagatca aa 1482

<210> 240

<211> 494

<212> PRT

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 3-271 VH-VL

<400> 240

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
100 105 110

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
130 135 140

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
145 150 155 160

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
165 170 175

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
180 185 190

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
195 200 205

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
210 215 220

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
225 230 235 240

135

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Gln
245 250 255

Leu Val Glu Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu Thr Leu Ser
260 265 270

Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
275 280 285

Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile
290 295 300

Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val
305 310 315 320

Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser
325 330 335

Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Pro
340 345 350

Asp Arg Met Gly His Gly Phe Asp Ile Trp Gly Gln Gly Thr Met Val
355 360 365

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
370 375 380

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

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile
405 410 415

Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Ser Gly Lys Ala Pro Lys
420 425 430

Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg
435 440 445

Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser
450 455 460

Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser
465 470 475 480

Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
485 490

<210> 241

<211> 1488

<212> DNA

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 4-10 VH-VL

<400> 241

gagctcgtga tgacacagtc tccatcctcc ctgactgtga cagcaggaga gaaggtcact 60

atgagctgca agtccagtca gagtctgtta aacagtggaa atcaaaagaa ctacttgacc 120

tggtaccagc agaaaccagg gcagcctcct aaactgttga tctactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240

atcagcagtg tgcaggctga agacctggca gtttattact gtcagaatga ttatagttat 300

ccgctcacgt tcggtgctgg gaccaagctt gagatcaaag gtggtggtgg ttctggcggc 360

ggcggctccg gtggtggtgg ttctgaggtg cagctgctcg agcagtctgg agctgagctg 420

gtaaggcctg ggacttcagt gaagatatcc tgcaaggctt ctggatacgc cttcactaac 480

tactggctag gttgggtaaa gcagaggcct ggacatggac ttgagtggat tggagatatt 540

ttccctggaa gtggtaatat ccactacaat gagaagttca agggcaaagc cacactgact 600

gcagacaaat cttcgagcac agcctatatg cagctcagta gcctgacatt tgaggactct 660

gctgtctatt tctgtgcaag actgaggaac tgggacgagc ctatggacta ctggggccaa 720

gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg agctgcagct ggtcgagtct 780

gggggaggct tggtacagcc tgggggtcc ctgagactct cctgtgcagc ctctggattc 840

acctttagca gctatgccat gggctgggtc cgccaggctc agggaaggg gctggagtgg 900

gtctcagctg ttagtggtag tggtggtagc acatactacg cagactccgt gaagggccgg 960

ttcaccatct ccagagacaa ttccaagaac acgctgtatc tgcaaatgaa cagcctgaga 1020

gccgaggaca cggccgtata ttactgtgcg aaagccaaat tcctgggcca ctactacggt 1080

atggacgtct ggggccaagg gaccacggtc accgtctcct caggtggtgg tggttctggc 1140

ggcggcggct ccggtggtgg tggttctgag ctccagatga cccagtctcc atcctccctg 1200

tctgcatctg taggagacag agtcaccatc acttgccggg caagtcagag cattagcagc 1260

tatttaaatt ggtatcagca gaaaccaggg aaagccccta agctcctgat ctatgctgca 1320

tccagtttgc aaagtggagt cccatcaagg ttcagcggca gtggatctgg gacagagttc 1380

actctcacaa tcagcagcct gcagcctgaa gattttgcaa cttattactg tcttcagcat 1440

aatgcttacc cgtacacttt cggccagggg accaaggtgg aaatcaaa 1488

<210> 242

<211> 496

<212> PRT

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 4-10 VH-VL

<400> 242

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
100 105 110

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
130 135 140

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
145 150 155 160

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
165 170 175

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
180 185 190

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
195 200 205

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
210 215 220

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
225 230 235 240

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Gln

245 250 255

Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg
260 265 270

Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ala Met Gly
275 280 285

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Val
290 295 300

Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg
305 310 315 320

Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met
325 330 335

Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Lys Ala
340 345 350

Lys Phe Leu Gly His Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr
355 360 365

Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
370 375 380

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

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln
405 410 415

Ser Ile Ser Ser Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
420 425 430

Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro
435 440 445

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile
450 455 460

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His
465 470 475 480

Asn Ala Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
485 490 495

<210> 243

<211> 1512

<212> DNA

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 4-48 VH-VL

<400> 243

gagctcgtga tgacacagtc tccatcctcc ctgactgtga cagcaggaga gaaggtcact 60

atgagctgca agtccagtca gagtctgtta aacagtggaa atcaaaagaa ctacttgacc 120

tggtaccagc agaaaccagg gcagcctcct aaactgttga tctactgggc atccactagg 180

gaatctgggg tccctgatcg cttcacaggc agtggatctg gaacagattt cactctcacc 240

atcagcagtg tgcaggctga agacctggca gtttattact gtcagaatga ttatagttat 300

ccgctcacgt tcggtgctgg gaccaagctt gagatcaaag gtggtggtgg ttctggcggc 360

ggcggctccg gtggtggtgg ttctgaggtg cagctgctcg agcagtctgg agctgagctg 420

gtaaggcctg ggacttcagt gaagatatcc tgcaaggctt ctggatacgc cttcactaac 480

tactggctag gttgggtaaa gcagaggcct ggacatggac ttgagtggat tggagatatt 540

ttccctggaa gtggtaatat ccactacaat gagaagttca agggcaaagc cacactgact 600

gcagacaaat cttcgagcac agcctatatg cagctcagta gcctgacatt tgaggactct 660

gctgtctatt tctgtgcaag actgaggaac tgggacgagc ctatggacta ctggggccaa 720

gggaccacgg tcaccgtctc ctcaggaggt ggtggatccg agctgcagct ggtcgagtct 780

ggtcctgtgc tggtgaaacc cacagatacc ctcacgctga cttgcaccgt ctctgggttc 840

tcactcaata atcctagaat gggtgtgagc tggatccgtc agccccccagg gaagaccctg 900

gagtggcttg cacacatttt tccgagtgac gcaaaagccc acagtgcatc tctgaagagc 960

aggctcacca tctccaagga cacctccaaa agccaggtgg tccctaccat gaccaacatg 1020

gaccctgtgg acacagccac atattactgt gcacggatat tgggggaata ctatccccca 1080

gcctggttcg acccctgggg ccagggaacc ctggtcaccg tctcctcagg tggtggtggt 1140

tctggcggcg gcggctccgg tggtggtggt tctgagctcg tgatgacaca gtctccagac 1200

tccctggctg tgtctctggg cgagagggcc accatcaact gcaagtccag ccagagtgtt 1260

ttatacagct ccaacaataa gaactactta gcttggtacc agcagaaacc aggacagcct 1320

cctaagctgc tcatttactg ggcatctacc cgggaatccg gggtccctga ccgattcagt 1380

ggcagcgggt ctgggacaga tttcactctc accatcagca gcctgcaggc tgaagacgtg 1440

gcagtttatt actgtcagca atatttgaaa atcccttata cttttggcca ggggaccaag 1500

gtggagatca aa 1512

<210> 244

<211> 504

<212> PRT

<213> artificial sequence

<220>

<223> anti-EpCAM 5-10 VL-VH x human anti-CD3 4-48 VH-VL

<400> 244

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

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

Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
100 105 110

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
130 135 140

Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Thr Asn
145 150 155 160

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Gly Leu Glu Trp
165 170 175

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
180 185 190

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
195 200 205

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
210 215 220

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
225 230 235 240

Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Gln
245 250 255

Leu Val Glu Ser Gly Pro Val Leu Val Lys Pro Thr Asp Thr Leu Thr
260 265 270

Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Asn Asn Pro Arg Met Gly
275 280 285

Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Thr Leu Glu Trp Leu Ala
290 295 300

His Ile Phe Pro Ser Asp Ala Lys Ala His Ser Ala Ser Leu Lys Ser
305 310 315 320

Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Ser Gln Val Val Pro Thr
325 330 335

Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
340 345 350

Ile Leu Gly Glu Tyr Tyr Pro Pro Ala Trp Phe Asp Pro Trp Gly Gln
355 360 365

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
370 375 380

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

Ser Leu Ala Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser
405 410 415

Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu Ala Trp
420 425 430

Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala
435 440 445

Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser
450 455 460

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val
465 470 475 480

Ala Val Tyr Tyr Cys Gln Gln Tyr Leu Lys Ile Pro Tyr Thr Phe Gly
485 490 495

Gln Gly Thr Lys Val Glu Ile Lys
500

<210> 245

<211> 1488

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD20 VL-VH x human anti-CD3 3-190 VH-VL

<400> 245

caaattgttc tctcccagtc tccagcaatc ctttctgcat ctccagggga gaaggtcaca 60

atgacttgca gggccagctc aagtttaagt ttcatgcact ggtaccagca gaagccagga 120

tcctccccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa 240

gatgctgcca cttatttctg ccatcagtgg agtagtaacc cgctcacgtt cggtgctggg 300

acaaaggtgg aaataaaagg tggtggtggt tctggcggcg gcggctccgg tggtggtggt 360

tctcaggtgc aactgcggca gcctggggct gagctggtga agcctggggc ctcagtgaag 420

atgtcctgca aggcttctgg ctacacattt accagttaca tatgcactg ggtaaagcag 480

acacctggac agggcctgga atggattgga gctatttatc caggaaatgg tgatacttcc 540

tacaatcaga agttcaaagg caaggccaca ttgactgcag acaaatcctc cagcacagcc 600

tacatgcagc tcagcagtct gacatctgag gactctgcgg tctattactg tgcaagatcg 660

cactacggta gtaactacgt agactacttt gactactggg gccaaggcac actagtcaca 720

gtctcgacag gaggtggtgg atccgagctg cagctggtcg agtggggcgc aggactgttg 780

aagccttcgg agaccctgtc cctcacctgc gctgtctatg gtgggtcctt cagtggttac 840

tactggagct ggatccgcca gcccccaggg aaggggctgg agtggattgg ggaaatcaat 900

catagtggaa gcaccaacta caacccgtcc ctcaagagtc gagtcaccat atcagtagac 960

acgtccaaga accagttctc cctgaagctg agctctgtga ccgccgcgga cacggctgtg 1020

tattactgtg cgagaggccg aggccgattt ttggggtggt tattaggggg ctccaactgg 1080

ttcgacccct ggggccaggg aaccctggtc accgtctcct caggtggtgg tggttctggc 1140

ggcggcggct ccggtggtgg tggttctgag ctcgtgatga cccagtctcc atcctccctg 1200

tctgcatctg taggagacag agtcaccatc acttgccggg cgagtcaggg cattagcaat 1260

tatttaaatt ggtatcagca gaaaccaggg aaagccccta agctcctgat ctacgatgca 1320

tccaatttgg aaacaggggt cccatcaagg ttcagtggca gtggatctgg gacagatttc 1380

actctcacca tcagcagtct gcaacctgaa gattttgcaa cttactactg tcaacagagt 1440

tacagtaccc cgtacacttt tggccagggg accaaagtgg atatcaaa 1488

<210> 246

<211> 496

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD20 VL-VH x human anti-CD3 3-190 VH-VL

<400> 246

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Leu Ser Phe Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

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

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

Asp Ala Ala Thr Tyr Phe Cys His Gln Trp Ser Ser Asn Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Arg Gln Pro
115 120 125

Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
130 135 140

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gln
145 150 155 160

Thr Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
165 170 175

Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr
180 185 190

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
195 200 205

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser His Tyr Gly Ser
210 215 220

Asn Tyr Val Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr

225 230 235 240

Val Ser Thr Gly Gly Gly Gly Ser Glu Leu Gln Leu Val Glu Trp Gly
245 250 255

Ala Gly Leu Leu Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala Val
260 265 270

Tyr Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser Trp Ile Arg Gln Pro
275 280 285

Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile Asn His Ser Gly Ser
290 295 300

Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp
305 310 315 320

Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala
325 330 335

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Gly Arg Phe Leu Gly
340 345 350

Trp Leu Leu Gly Gly Ser Asn Trp Phe Asp Pro Trp Gly Gln Gly Thr
355 360 365

Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
370 375 380

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

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln
405 410 415

Gly Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala
420 425 430

Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro
435 440 445

Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
450 455 460

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser
465 470 475 480

Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
485 490 495

<210> 247

<211> 1470

<212> DNA

<213> artificial sequence

<220>

<223> anti-CD20 VL-VH x human anti-CD3 3-148 VH-VL

<400> 247

caaattgttc tctcccagtc tccagcaatc ctttctgcat ctccagggga gaaggtcaca 60

atgacttgca gggccagctc aagtttaagt ttcatgcact ggtaccagca gaagccagga 120

tcctcccca aaccctggat ttatgccaca tccaacctgg cttctggagt ccctgctcgc 180

ttcagtggca gtgggtctgg gacctcttac tctctcacaa tcagcagagt ggaggctgaa 240

gatgctgcca cttatttctg ccatcagtgg agtagtaacc cgctcacgtt cggtgctggg 300

acaaaggtgg aaataaaagg tggtggtggt tctggcggcg gcggctccgg tggtggtggt 360

tctcaggtgc aactgcggca gcctggggct gagctggtga agcctggggc ctcagtgaag 420

atgtcctgca aggcttctgg ctacacattt accagttaca tatgcactg ggtaaagcag 480

acacctggac agggcctgga atggattgga gctatttatc caggaaatgg tgatacttcc 540

tacaatcaga agttcaaagg caaggccaca ttgactgcag acaaatcctc cagcacagcc 600

tacatgcagc tcagcagtct gacatctgag gactctgcgg tctattactg tgcaagatcg 660

cactacggta gtaactacgt agactacttt gactactggg gccaaggcac actagtcaca 720

gtctcgacag gaggtggtgg atccgagctg cagctggtcg agtctggccc aggactggtg 780

aagccttcgg ggaccctgtc cctcacctgc gctgtctctg gtggctccat cagcagtaga 840

aactggtgga gttgggtccg ccagccccca gggaaggggc tggagtggat tggtgatatc 900

tatcatagtg ggagcaccaa ctacaacccg tccctcaaga gtcgagtcac catatcagta 960

gacaagtcca agaaccagtt ctccctgaag ctgagctctg tgaccgccgc ggacacggcc 1020

gtgtattact gtgcgagtgg gtataccagc tgtcgtgatg cttttgatat ctggggccaa 1080

gggacaatgg tcaccgtctc ctcaggtggt ggtggttctg gcggcggcgg ctccggtggt 1140

ggtggttctg agctcgtgat gactcagtct ccatcctccc tgtctgcatc tgtaggagac 1200

agagtcacca tcacttgccg ggcgagtcag ggcattggca attatttagc ctggtatcag 1260

cagaaaccag ggcagcctcc taagatgctc atttactggg catcaatccg ggaatccggg 1320

gtccctgacc gattcagtgg cagcgggtct gggacagact tcactctcac catcagcagc 1380

ctgcaggctg aagatgtggc agtttactac tgtcagcaat attatagtaa tcctcagacg 1440

ttcggccaag ggaccaaggt ggaaatcaaa 1470

<210> 248

<211> 490

<212> PRT

<213> artificial sequence

<220>

<223> anti-CD20 VL-VH x human anti-CD3 3-148 VH-VL

<400> 248

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

Glu Lys Val Thr Met Thr Cys Arg Ala Ser Ser Ser Leu Ser Phe Met
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Ser Ser Pro Lys Pro Trp Ile Tyr
35 40 45

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

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

Asp Ala Ala Thr Tyr Phe Cys His Gln Trp Ser Ser Asn Pro Leu Thr
85 90 95

Phe Gly Ala Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Arg Gln Pro
115 120 125

Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Met Ser Cys Lys
130 135 140

Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Asn Met His Trp Val Lys Gln
145 150 155 160

Thr Pro Gly Gln Gly Leu Glu Trp Ile Gly Ala Ile Tyr Pro Gly Asn
165 170 175

Gly Asp Thr Ser Tyr Asn Gln Lys Phe Lys Gly Lys Ala Thr Leu Thr
180 185 190

Ala Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr
195 200 205

Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser His Tyr Gly Ser
210 215 220

Asn Tyr Val Asp Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
225 230 235 240

Val Ser Thr Gly Gly Gly Gly Ser Glu Leu Gln Leu Val Glu Ser Gly
245 250 255

Pro Gly Leu Val Lys Pro Ser Gly Thr Leu Ser Leu Thr Cys Ala Val
260 265 270

Ser Gly Gly Ser Ile Ser Ser Arg Asn Trp Trp Ser Trp Val Arg Gln
275 280 285

Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Asp Ile Tyr His Ser Gly
290 295 300

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

Asp Lys Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala
325 330 335

Ala Asp Thr Ala Val Tyr Tyr Cys Ala Ser Gly Tyr Thr Ser Cys Arg
340 345 350

Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
355 360 365

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
370 375 380

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

Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Gly Asn Tyr Leu
405 410 415

Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Met Leu Ile Tyr
420 425 430

Trp Ala Ser Ile Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
435 440 445

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu
450 455 460

Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Asn Pro Gln Thr
465 470 475 480

Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
485 490

<210> 249

<211> 1491

<212> DNA

<213> artificial sequence

<220>

<223> anti-CCR5 VL-VH x human anti-CD3 3-190 VH-VL

<400> 249

gacattatcc tgatccaatc tccaccttct ttggctgtgt ctctagggca gagggccacc 60

atctcctgca gaaccagcga aaatgttgac ggatacggca ttagttttat aaactggtac 120

caacagaagc caggacagcc acccaaactc ctcatctatg ctgcatccca ccaaggatcc 180

ggggtccctg ccagatttag tggcagtggg tctgggacag acttcagcct caacatccat 240

cctttggagg aggatgatac tgcaatgtat ttctgtcacc aaagtaagaa ggttccgtgg 300

acgttcggtg gaggcaccaa gctggaaatc aaaggtggtg gtggttctgg cggcggcggc 360

tccggtggtg gtggttctca gctggagcag tctggacctg aactgaagaa gcctggagag 420

acagtcacga tctcctgcaa ggcttctggg tataccttca cgaagttcgg aatgaactgg 480

gtgaagcagg ctccaggaaa gggtttaaag tggatgggct ggatacacac ctccactgga 540

gagccaacat attctgatga cttcaaggga cggtttgcct tctctttgga aacgtctgcc 600

agcactgcct atttgcggat caacaacctc aaaaatgagg acatggctaa atacttctgt 660

gccagaggtg gtccttacgt aaggggtgct ttggactact ggggtcaagg aacctcagtc 720

accgtctcct ccggaggtgg tggatccgag ctgcagctgg tcgagtgggg cgcaggactg 780

ttgaagcctt cggagaccct gtccctcacc tgcgctgtct atggtgggtc cttcagtggt 840

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aattatttaa attggtatca gcagaaacca gggaaagccc ctaagctcct gatctacgat 1320

gcatccaatt tggaaacagg ggtcccatca aggttcagtg gcagtggatc tgggacagat 1380

ttcactctca ccatcagcag tctgcaacct gaagattttg caacttacta ctgtcaacag 1440

agttacagta ccccgtacac ttttggccag gggaccaaag tggatatcaa a 1491

<210> 250

<211> 497

<212> PRT

<213> artificial sequence

<220>

<223> anti-CCR5 VL-VH x human anti-CD3 3-190 VH-VL

<400> 250

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

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

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

Lys Leu Leu Ile Tyr Ala Ala Ser His Gln Gly Ser Gly Val Pro Ala
50 55 60

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

Pro Leu Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys His Gln Ser Lys
85 90 95

Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Leu
115 120 125

Glu Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Thr Ile
130 135 140

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Lys Phe Gly Met Asn Trp
145 150 155 160

Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp Ile His
165 170 175

Thr Ser Thr Gly Glu Pro Thr Tyr Ser Asp Asp Phe Lys Gly Arg Phe
180 185 190

Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Arg Ile Asn
195 200 205

Asn Leu Lys Asn Glu Asp Met Ala Lys Tyr Phe Cys Ala Arg Gly Gly
210 215 220

Pro Tyr Val Arg Gly Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val
225 230 235 240

Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Gln Leu Val Glu Trp
245 250 255

Gly Ala Gly Leu Leu Lys Pro Ser Glu Thr Leu Ser Leu Thr Cys Ala
260 265 270

Val Tyr Gly Gly Ser Phe Ser Gly Tyr Tyr Trp Ser Trp Ile Arg Gln
275 280 285

Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Glu Ile Asn His Ser Gly
290 295 300

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

Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala
325 330 335

Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Gly Arg Phe Leu
340 345 350

Gly Trp Leu Leu Gly Gly Ser Asn Trp Phe Asp Pro Trp Gly Gln Gly
355 360 365

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
370 375 380

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

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
405 410 415

Gln Gly Ile Ser Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
420 425 430

Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val
435 440 445

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
450 455 460

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
465 470 475 480

Ser Tyr Ser Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp Ile
485 490 495

Lys

<210> 251

<211> 1473

<212> DNA

<213> artificial sequence

<220>

<223> anti-CCR5 VL-VH x human anti-CD3 3-148 VH-VL

<400> 251

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caacagaagc caggacagcc acccaaactc ctcatctatg ctgcatccca ccaaggatcc 180

ggggtccctg ccagatttag tggcagtggg tctgggacag acttcagcct caacatccat 240

cctttggagg aggatgatac tgcaatgtat ttctgtcacc aaagtaagaa ggttccgtgg 300

acgttcggtg gaggcaccaa gctggaaatc aaaggtggtg gtggttctgg cggcggcggc 360

tccggtggtg gtggttctca gctggagcag tctggacctg aactgaagaa gcctggagag 420

acagtcacga tctcctgcaa ggcttctggg tataccttca cgaagttcgg aatgaactgg 480

gtgaagcagg ctccaggaaa gggtttaaag tggatgggct ggatacacac ctccactgga 540

gagccaacat attctgatga cttcaaggga cggtttgcct tctctttgga aacgtctgcc 600

agcactgcct atttgcggat caacaacctc aaaaatgagg acatggctaa atacttctgt 660

gccagaggtg gtccttacgt aaggggtgct ttggactact ggggtcaagg aacctcagtc 720

accgtctcct ccggaggtgg tggatccgag ctgcagctgg tcgagtctgg cccaggactg 780

gtgaagcctt cggggaccct gtccctcacc tgcgctgtct ctggtggctc catcagcagt 840

agaaactggt ggagttgggt ccgccagccc ccagggaagg ggctggagtg gattggtgat 900

atctatcata gtgggagcac caactacaac ccgtccctca agagtcgagt caccatatca 960

gtagacaagt ccaagaacca gttctccctg aagctgagct ctgtgaccgc cgcggacacg 1020

gccgtgtatt actgtgcgag tgggtatacc agctgtcgtg atgcttttga tatctggggc 1080

caagggacaa tggtcaccgt ctcctcaggt ggtggtggtt ctggcggcgg cggctccggt 1140

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cagcagaaac cagggcagcc tcctaagatg ctcatttact gggcatcaat ccgggaatcc 1320

ggggtccctg accgattcag tggcagcggg tctgggacag acttcactct caccatcagc 1380

agcctgcagg ctgaagatgt ggcagtttac tactgtcagc aatattatag taatcctcag 1440

acgttcggcc aagggaccaa ggtggaaatc aaa 1473

<210> 252

<211> 491

<212> PRT

<213> artificial sequence

<220>

<223> anti-CCR5 VL-VH x human anti-CD3 3-148 VH-VL

<400> 252

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

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

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

Lys Leu Leu Ile Tyr Ala Ala Ser His Gln Gly Ser Gly Val Pro Ala
50 55 60

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

Pro Leu Glu Glu Asp Asp Thr Ala Met Tyr Phe Cys His Gln Ser Lys
85 90 95

Lys Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Gly
100 105 110

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Leu
115 120 125

Glu Gln Ser Gly Pro Glu Leu Lys Lys Pro Gly Glu Thr Val Thr Ile
130 135 140

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Lys Phe Gly Met Asn Trp
145 150 155 160

Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly Trp Ile His
165 170 175

Thr Ser Thr Gly Glu Pro Thr Tyr Ser Asp Asp Phe Lys Gly Arg Phe
180 185 190

Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Arg Ile Asn
195 200 205

Asn Leu Lys Asn Glu Asp Met Ala Lys Tyr Phe Cys Ala Arg Gly Gly
210 215 220

Pro Tyr Val Arg Gly Ala Leu Asp Tyr Trp Gly Gln Gly Thr Ser Val
225 230 235 240

Thr Val Ser Ser Gly Gly Gly Gly Ser Glu Leu Gln Leu Val Glu Ser
245 250 255

Gly Pro Gly Leu Val Lys Pro Ser Gly Thr Leu Ser Leu Thr Cys Ala
260 265 270

Val Ser Gly Gly Ser Ile Ser Ser Arg Asn Trp Trp Ser Trp Val Arg
275 280 285

Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Asp Ile Tyr His Ser
290 295 300

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

Val Asp Lys Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val Thr
325 330 335

Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Ser Gly Tyr Thr Ser Cys
340 345 350

Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser
355 360 365

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
370 375 380

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

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

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Met Leu Ile
420 425 430

Tyr Trp Ala Ser Ile Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
435 440 445

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala
450 455 460

Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Ser Asn Pro Gln
465 470 475 480

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
485 490