TITLE OF THE INVENTION

Human binding molecules capable of neutralizing influenza virus H5N1 and uses thereof

FIELD OF THE INVENTION

The invention relates to medicine. In particular, the invention relates to the diagnosis, prophylaxis and/or treatment of an infection by influenza virus H5N1.

BACKGROUND OF THE INVENTION

Influenza viruses consist of three types, A, B and C. Influenza A viruses infect a wide variety of birds and mammals, including humans, horses, marine mammals, pigs, ferrets, and chickens. In animals most influenza A viruses cause mild localized infections of the respiratory and intestinal tract. However, highly pathogenic influenza A strains such as H5N1 exist that cause systemic infections in poultry in which mortality may reach 100%. Animals infected with influenza A often act as a reservoir for the influenza viruses and certain subtypes have been shown to cross the species barrier to humans.

Influenza A viruses can be classified into subtypes based on allelic variations in antigenic regions of two genes that encode surface glycoproteins, namely, hemagglutinin (HA) and neuraminidase (NA) which are required for viral attachment and cellular release. Other major viral proteins include the nucleoprotein, the nucleocapsid structural protein, membrane proteins (M1 and M2), polymerases (PA, PB and PB2) and non-structural proteins (NS1 and NS2).

Currently, sixteen subtypes of HA (H1-H16) and nine NA (N1-N9) antigenic variants are known in influenza A virus. Previously, only three subtypes have been known to circulate in humans (H1N1, H1N2, and H3N2). However, in recent years, the pathogenic H5N1 subtype of avian influenza A has been reported to cross the species barrier and infect humans as documented in Hong Kong in 1997 and 2003, leading to the death of several patients.

In humans, the avian influenza virus infects cells of the respiratory tract as well as the intestinal tract, liver, spleen, kidneys and other organs. Symptoms of avian influenza infection include fever, respiratory difficulties including shortness of breath and cough, lymphopenia, diarrhea and difficulties regulating blood sugar levels. In contrast to seasonal influenza the group most at risk are healthy adults which make up the bulk of the population.Due to the

high pathogenicity of certain avian influenza A subtypes, particularly H5N1, and their demonstrated ability to cross over to infect humans, there is a significant economic and public health risk associated with these viral strains, including a real epidemic and pandemic threat. The scale of the threat is illustrated by the 1918 influenza pandemic which killed over 50 million people.

Currently, no effective vaccines for H5N1 infection are available, so passive immunotherapy with immunoglobulins may be an alternative strategy. Use of passive immunization during the 1918 pandemic reportedly halved the death rate. In view of their therapeutic benefit in humans, there is thus a need for binding molecules, preferably human binding molecules, capable of neutralizing H5N1. The present invention provides these binding molecules and shows that they can be used in medicine, in particular for diagnosis, prevention and/or treatment of H5N1 infections.

DESCRIPTION OF THE FIGURES

In Fig 1 immunoblot analysis of different hemagglutinins (HAs) using antibodies CR6307 (left part), CR6323 (middle part) and CR5111 (right part) is presented. Recombinant HAs were subjected to reducing SDS-PAGE analysis and immunoblot analysis. In lanes 1 sHA of H5N1TV is shown; in lanes 2 recombinant HA, subtype H5 (A/Vietnam/1203/2004 (H5N1)) is shown; in lanes 3 recombinant HA, subtype H3 (A/Wyoming/3/2003(H3N2)) is shown; and in lanes 4 recombinant HA, subtype H1 (A/New Caledonia/20/99 (H1N1)) is shown. The position where HA0, HA1 and HA2 can be found is also indicated.

Fig 2 shows the average clinical score per group of mice in a study (example 12) wherein, one day before infection with influenza H5N1 virus, mice were prophylactically treated with three human H5N1 monoclonal antibodies CR6261, CR6323, and CR6325, in different doses.

Fig 3 shows the change in body weight during the prophylactic treatment of mice with anti-H5N1 antibodies during 21 days post-infection (example 12).

Fig 4 shows the number of surviving mice in the different groups in the study of Fig 2 and 3 (example 12).

Fig 5 shows the mortality rate in relation to the dose given of the anti-H5N1 antibodies in the study of Figs 2-4 (example 12).

Fig 6 shows the average clinical score per group of mice in a study (example 13) wherein mice were infected with a lethal dose of H5N1 influenza virus and treated at different time points after infection (4 hr, 1, 2 and 3 days) with CR6261 anti-H5N1 monoclonal antibody, or a non-related antibody CR2006 (administered at day 1 post-infection).

Fig 7 shows the number of surviving animals in each group of the study described in fig 6. All animals of group 1-4, except for one animal in group 1 survived the entire study up to day 21 post-infection. All animals of group 5 had died at day 9.

Fig 8 shows the average body weight of the mice in each group during the study as described for fig 6. Measuring the body weight of the mice in group 5 stopped at day 9 as all mice in that group had died by that time. All remaining mice in groups 1-4 reached normal levels of body weight at day 21 post-infection, although it depended on the time of treatment how fast each group recovered.

Fig 9 shows the percentage of surviving animals in each group of a study wherein mice were infected with a lethal dose of H1N1 influenza virus and treated at different time points (1 day prior-, 1, 2 and 3 days post-infection) with CR6261 anti-H5N1 monoclonal antibody, or a non-related antibody CR57 (administered at day 1 post-infection).

Fig 10 shows the average body weight of the mice in each group during the study as described for fig 9. Measuring the body weight of the mice in group 5 stopped at day 9 as all mice in that group had died by that time. All remaining mice in groups 1-4 reached normal levels of body weight at day 21 post-infection, although it depended on the time of treatment how fast each group recovered.

DESCRIPTION OF THE INVENTION

Here below follow definitions of terms as used in the invention.

As used herein the term "binding molecule" refers to an intact immunoglobulin including monoclonal antibodies, such as chimeric, humanized or human monoclonal antibodies, or to an antigen-binding and/or variable domain comprising fragment of an immunoglobulin that competes with the intact immunoglobulin for specific binding to the binding partner of the immunoglobulin, *e.g.* H5N1. Regardless of structure, the antigen-binding fragment binds with the same antigen that is recognized by the intact immunoglobulin. An antigen-binding fragment can comprise a peptide or polypeptide

comprising an amino acid sequence of at least 2, 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175, 200, or 250 contiguous amino acid residues of the amino acid sequence of the binding molecule.

The term "binding molecule", as used herein includes all immunoglobulin classes and subclasses known in the art. Depending on the amino acid sequence of the constant domain of their heavy chains, binding molecules can be divided into the five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgA1, IgA2, IgG1, IgG2, IgG3 and IgG4.

Antigen-binding fragments include, *inter alia*, Fab, F(ab'), F(ab')2, Fv, dAb, Fd, complementarity determining region (CDR) fragments, single-chain antibodies (scFv), bivalent single-chain antibodies, single-chain phage antibodies, diabodies, triabodies, tetrabodies, (poly)peptides that contain at least a fragment of an immunoglobulin that is sufficient to confer specific antigen binding to the (poly)peptide, etc. The above fragments may be produced synthetically or by enzymatic or chemical cleavage of intact immunoglobulins or they may be genetically engineered by recombinant DNA techniques. The methods of production are well known in the art and are described, for example, in Antibodies: A Laboratory Manual, Edited by: E. Harlow and D, Lane (1988), Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, which is incorporated herein by reference. A binding molecule or antigen-binding fragment thereof may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or they may be different.

The binding molecule can be a naked or unconjugated binding molecule but can also be part of an immunoconjugate. A naked or unconjugated binding molecule is intended to refer to a binding molecule that is not conjugated, operatively linked or otherwise physically or functionally associated with an effector moiety or tag, such as *inter alia* a toxic substance, a radioactive substance, a liposome, an enzyme. It will be understood that naked or unconjugated binding molecules do not exclude binding molecules that have been stabilized, multimerized, humanized or in any other way manipulated, other than by the attachment of an effector moiety or tag. Accordingly, all post-translationally modified naked and unconjugated binding molecules are included herewith, including where the modifications are made in the natural binding molecule-producing cell environment, by a recombinant binding molecule-

producing cell, and are introduced by the hand of man after initial binding molecule preparation. Of course, the term naked or unconjugated binding molecule does not exclude the ability of the binding molecule to form functional associations with effector cells and/or molecules after administration to the body, as some of such interactions are necessary in order to exert a biological effect. The lack of associated effector group or tag is therefore applied in definition to the naked or unconjugated binding molecule *in vitro*, not *in vivo*.

As used herein, the term "biological sample" encompasses a variety of sample types, including blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures, or cells derived there from and the progeny thereof. The term also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components, such as proteins or polynucleotides. The term encompasses various kinds of clinical samples obtained from any species, and also includes cells in culture, cell supernatants and cell lysates.

The term "complementarity determining regions" (CDR) as used herein means sequences within the variable regions of binding molecules, such as immunoglobulins, that usually contribute to a large extent to the antigen binding site which is complementary in shape and charge distribution to the epitope recognized on the antigen. The CDR regions can be specific for linear epitopes, discontinuous epitopes, or conformational epitopes of proteins or protein fragments, either as present on the protein in its native conformation or, in some cases, as present on the proteins as denatured, *e.g.*, by solubilization in SDS. Epitopes may also consist of posttranslational modifications of proteins.

The term "deletion", as used herein, denotes a change in either amino acid or nucleotide sequence in which one or more amino acid or nucleotide residues, respectively, are absent as compared to the parent, often the naturally occurring, molecule.

The term "expression-regulating nucleic acid sequence" as used herein refers to polynucleotide sequences necessary for and/or affecting the expression of an operably linked coding sequence in a particular host organism. The expression-regulating nucleic acid

sequences, such as *inter alia* appropriate transcription initiation, termination, promoter, enhancer sequences; repressor or activator sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (*e.g.*, ribosome binding sites); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion, can be any nucleic acid sequence showing activity in the host organism of choice and can be derived from genes encoding proteins, which are either homologous or heterologous to the host organism. The identification and employment of expression-regulating sequences is routine to the person skilled in the art.

The term "functional variant", as used herein, refers to a binding molecule that comprises a nucleotide and/or amino acid sequence that is altered by one or more nucleotides and/or amino acids compared to the nucleotide and/or amino acid sequences of the parental binding molecule and that is still capable of competing for binding to the binding partner, *e.g.* H5N1, with the parental binding molecule. In other words, the modifications in the amino acid and/or nucleotide sequence of the parental binding molecule do not significantly affect or alter the binding characteristics of the binding molecule encoded by the nucleotide sequence or containing the amino acid sequence, *i.e.* the binding molecule is still able to recognize and bind its target. The functional variant may have conservative sequence modifications including nucleotide and amino acid substitutions, additions and deletions. These modifications can be introduced by standard techniques known in the art, such as site-directed mutagenesis and random PCR-mediated mutagenesis, and may comprise natural as well as non-natural nucleotides and amino acids.

Conservative amino acid substitutions include the ones in which the amino acid residue is replaced with an amino acid residue having similar structural or chemical properties. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), non-polar side chains (*e.g.*, glycine, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*,

tyrosine, phenylalanine, tryptophan). It will be clear to the skilled artisan that other classifications of amino acid residue families than the one used above can also be employed. Furthermore, a variant may have non-conservative amino acid substitutions, *e.g.*, replacement of an amino acid with an amino acid residue having different structural or chemical properties. Similar minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing immunological activity may be found using computer programs well known in the art.

A mutation in a nucleotide sequence can be a single alteration made at a locus (a point mutation), such as transition or transversion mutations, or alternatively, multiple nucleotides may be inserted, deleted or changed at a single locus. In addition, one or more alterations may be made at any number of loci within a nucleotide sequence. The mutations may be performed by any suitable method known in the art.

The term "host", as used herein, is intended to refer to an organism or a cell into which a vector such as a cloning vector or an expression vector has been introduced. The organism or cell can be prokaryotic or eukaryotic. It should be understood that this term is intended to refer not only to the particular subject organism or cell but to the progeny of such an organism or cell as well. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent organism or cell, but are still included within the scope of the term "host" as used herein.

The term "human", when applied to binding molecules as defined herein, refers to molecules that are either directly derived from a human or based upon a human sequence. When a binding molecule is derived from or based on a human sequence and subsequently modified, it is still to be considered human as used throughout the specification. In other words, the term human, when applied to binding molecules is intended to include binding molecules having variable and constant regions derived from human germline immunoglobulin sequences or based on variable or constant regions occurring in a human or human lymphocyte and modified in some form. Thus, the human binding molecules may include amino acid residues

not encoded by human germline immunoglobulin sequences, comprise substitutions and/or deletions (*e.g.*, mutations introduced by for instance random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). "Based on" as used herein refers to the situation that a nucleic acid sequence may be exactly copied from a template, or with minor mutations, such as by error-prone PCR methods, or synthetically made matching the template exactly or with minor modifications. Semi-synthetic molecules based on human sequences are also considered to be human as used herein.

The term "insertion", also known as the term "addition", denotes a change in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid or nucleotide residues, respectively, as compared to the parent sequence.

The term "isolated", when applied to binding molecules as defined herein, refers to binding molecules that are substantially free of other proteins or polypeptides, particularly free of other binding molecules having different antigenic specificities, and are also substantially free of other cellular material and/or chemicals. For example, when the binding molecules are recombinantly produced, they are preferably substantially free of culture medium, and when the binding molecules are produced by chemical synthesis, they are preferably substantially free of chemical precursors or other chemicals, *i.e.*, they are separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. The term "isolated" when applied to nucleic acid molecules encoding binding molecules as defined herein, is intended to refer to nucleic acid molecules in which the nucleotide sequences encoding the binding molecules are free of other nucleotide sequences, particularly nucleotide sequences encoding binding molecules that bind binding partners other than H5N1. Furthermore, the term "isolated" refers to nucleic acid molecules that are substantially separated from other cellular components that naturally accompany the native nucleic acid molecule in its natural host, *e.g.*, ribosomes, polymerases, or genomic sequences with which it is naturally associated. Moreover, "isolated" nucleic acid molecules, such as cDNA molecules, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

The term "monoclonal antibody" as used herein refers to a preparation of antibody molecules of single molecular composition. A monoclonal antibody displays a single binding specificity and affinity for a particular epitope. Accordingly, the term "human monoclonal antibody" refers to an antibody displaying a single binding specificity which has variable and constant regions derived from or based on human germline immunoglobulin sequences or derived from completely synthetic sequences. The method of preparing the monoclonal antibody is not relevant.

The term "naturally occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory is naturally occurring.

The term "nucleic acid molecule" as used in the present invention refers to a polymeric form of nucleotides and includes both sense and anti-sense strands of RNA, cDNA, genomic DNA, and synthetic forms and mixed polymers of the above. A nucleotide refers to a ribonucleotide, deoxynucleotide or a modified form of either type of nucleotide. The term also includes single- and double-stranded forms of DNA. In addition, a polynucleotide may include either or both naturally occurring and modified nucleotides linked together by naturally occurring and/or non-naturally occurring nucleotide linkages. The nucleic acid molecules may be modified chemically or biochemically or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those of skill in the art. Such modifications include, for example, labels, methylation, substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoramidates, carbamates, etc.), charged linkages (*e.g.*, phosphorothioates, phosphorodithioates, etc.), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen, etc.), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids, etc.). The above term is also intended to include any topological conformation, including single-stranded, double-stranded, partially duplexed, triplex, hairpinned, circular and padlocked conformations. Also included are synthetic molecules that

mimic polynucleotides in their ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules are known in the art and include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule. A reference to a nucleic acid sequence encompasses its complement unless otherwise specified. Thus, a reference to a nucleic acid molecule having a particular sequence should be understood to encompass its complementary strand, with its complementary sequence. The complementary strand is also useful, *e.g.*, for anti-sense therapy, hybridisation probes and PCR primers.

The term "operably linked" refers to two or more nucleic acid sequence elements that are usually physically linked and are in a functional relationship with each other. For instance, a promoter is operably linked to a coding sequence, if the promoter is able to initiate or regulate the transcription or expression of a coding sequence, in which case the coding sequence should be understood as being "under the control of" the promoter.

By "pharmaceutically acceptable excipient" is meant any inert substance that is combined with an active molecule such as a drug, agent, or binding molecule for preparing an agreeable or convenient dosage form. The "pharmaceutically acceptable excipient" is an excipient that is non-toxic to recipients at the dosages and concentrations employed, and is compatible with other ingredients of the formulation comprising the drug, agent or binding molecule. Pharmaceutically acceptable excipients are widely applied in the art.

The term "specifically binding", as used herein, in reference to the interaction of a binding molecule, *e.g.* an antibody, and its binding partner, *e.g.* an antigen, means that the interaction is dependent upon the presence of a particular structure, *e.g.* an antigenic determinant or epitope, on the binding partner. In other words, the antibody preferentially binds or recognizes the binding partner even when the binding partner is present in a mixture of other molecules or organisms. The binding may be mediated by covalent or non-covalent interactions or a combination of both. In yet other words, the term "specifically binding" means immunospecifically binding to an antigen or a fragment thereof and not immunospecifically binding to other antigens. A binding molecule that immunospecifically binds to an antigen

may bind to other peptides or polypeptides with lower affinity as determined by, *e.g.*, radioimmunoassays (RIA), enzyme-linked immunosorbent assays (ELISA), BIACORE, or other assays known in the art. Binding molecules or fragments thereof that immunospecifically bind to an antigen may be cross-reactive with related antigens. Preferably, binding molecules or fragments thereof that immunospecifically bind to an antigen do not cross-react with other antigens.

A "substitution", as used herein, denotes the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

The term "therapeutically effective amount" refers to an amount of the binding molecule as defined herein that is effective for preventing, ameliorating and/or treating a condition resulting from infection with H5N1.

The term "treatment" refers to therapeutic treatment as well as prophylactic or preventative measures to cure or halt or at least retard disease progress. Those in need of treatment include those already inflicted with a condition resulting from infection with H5N1 as well as those in which infection with H5N1 is to be prevented. Subjects partially or totally recovered from infection with H5N1 might also be in need of treatment. Prevention encompasses inhibiting or reducing the spread of H5N1 or inhibiting or reducing the onset, development or progression of one or more of the symptoms associated with infection with H5N1.

The term "vector" denotes a nucleic acid molecule into which a second nucleic acid molecule can be inserted for introduction into a host where it will be replicated, and in some cases expressed. In other words, a vector is capable of transporting a nucleic acid molecule to which it has been linked. Cloning as well as expression vectors are contemplated by the term "vector", as used herein. Vectors include, but are not limited to, plasmids, cosmids, bacterial artificial chromosomes (BAC) and yeast artificial chromosomes (YAC) and vectors derived from bacteriophages or plant or animal (including human) viruses. Vectors comprise an origin of replication recognized by the proposed host and in case of expression vectors, promoter and other regulatory regions recognized by the host. A vector containing a second nucleic acid

molecule is introduced into a cell by transformation, transfection, or by making use of viral entry mechanisms. Certain vectors are capable of autonomous replication in a host into which they are introduced (*e.g.*, vectors having a bacterial origin of replication can replicate in bacteria). Other vectors can be integrated into the genome of a host upon introduction into the host, and thereby are replicated along with the host genome.

SUMMARY OF THE INVENTION

The invention provides human binding molecules capable of specifically binding to influenza virus H5N1 and exhibiting neutralizing activity against H5N1. The invention also provides binding molecules that bind to an epitope in the haemagglutinin protein that is shared between influenza subtypes and therefore relates to binding molecules that cross-react between H5-, H1-, H2-, H6- and H9 influenza based subtypes, such as H5N1, H1N1 and other influenza strains that contain the HA protein with these particular epitopes. The invention also pertains to nucleic acid molecules encoding at least the binding region of the human binding molecules. The invention further provides for the use of the human binding molecules of the invention in the prophylaxis and/or treatment of a subject having, or at risk of developing, an H5N1 infection. Besides that, the invention pertains to the use of the human binding molecules of the invention in the diagnosis/detection of H5N1.

DETAILED DESCRIPTION

In a first aspect the present invention encompasses binding molecules capable of specifically binding to influenza virus A, particularly influenza virus A subtype H5N1. Preferably, the binding molecules are human binding molecules. Preferably, the binding molecules of the invention exhibit neutralizing activity against influenza virus A subtype H5N1. In a further aspect the binding molecules of the invention are capable of specifically binding to and/or have neutralizing activity against different influenza virus H5N1 strains. These strains may be a member of influenza virus H5N1 strains of clade 1, clade 2 or clade 3. Phylogenetic analyses of the HA genes from the 2004 and 2005 H5N1 outbreak showed two different lineages of HA genes, termed clades 1 and 2. Viruses in each of these clades are distributed in non-overlapping geographic regions of Asia. The H5N1 viruses from the Indochina peninsula are tightly clustered within clade 1, whereas H5N1 isolates from several surrounding

countries are distinct from clade 1 isolates and belong in the more divergent clade 2. Clade 1 H5N1 viruses were isolated from humans and birds in Vietnam, Thailand, and Cambodia, but only from birds in Laos and Malaysia. The clade 2 viruses were found in viruses isolated exclusively from birds in China, Indonesia, Japan, and South Korea. Viruses isolated from birds and humans in Hong Kong in 2003 and 1997 made up clades 1′ (also categorized in clade 1) and 3, respectively (see WHO Global Influenza Program Surveillance Network, 2005). The hemagglutinins of the clades differ in their amino acid sequences. Examples of clade 1 strains include, but are not limited to, A/Hong Kong/213/03, A/Vietnam/1194/04, A/Vietnam/1203/04 and A/Thailand/1(KAN-1)/2004. Examples of clade 2 strains include, but are not limited to, A/Indonesia/5/05, A/bar headed goose/Qinghai/1A/05, A/turkey/Turkey/1/05 and A/Anhui/1/05. Examples of clade 3 strains include, but are not limited to, A/Hong Kong/156/97 and A/goose/Guangdong/1/96. Other strains can be found, *e.g.*, in WHO Global Influenza Program Surveillance Network, 2005 and on http://www.who.int/csr/disease/avian_influenza/guidelines/recommendationvaccine.pdf Preferably, the binding molecules of the invention are capable of specifically binding to and have neutralizing activity against clade 1, clade 2 and clade 3 strains. The binding molecules of the invention may be capable of specifically binding to influenza virus H5N1 that are viable, living and/or infective or that are in inactivated/attenuated form. Methods for inactivating/attenuating influenza virus H5N1 are well known in the art and include, but are not limited to, treatment with formalin, β-propiolactone (BPL), merthiolate, and/or ultraviolet light.

The binding molecules of the invention may also be capable of specifically binding to one or more fragments of influenza virus H5N1 such as *inter alia* a preparation of one or more proteins and/or (poly)peptides derived from subtype H5N1 or one or more recombinantly produced proteins and/or polypeptides of H5N1. For methods of treatment and/or prevention of H5N1 infections the binding molecules are preferably capable of specifically binding to surface accessible proteins of H5N1 such as the surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), which are required for viral attachment and cellular release, or membrane proteins (M1 and M2). In a specific embodiment the binding molecules of the invention are capable of specifically binding to the HA molecule of H5N1 strains. They may be capable of specifically binding to the HA1 and/or HA2 subunit of the

HA molecule. They may be capable of specifically binding to linear or structural and/or conformational epitopes on the HA1 and/or HA2 subunit of the HA molecule. The HA molecule may be purified from viruses or recombinantly produced and optionally isolated before use. Alternatively, HA may be expressed on the surface of cells.

For diagnostical purposes the binding molecules may also be capable of specifically binding to proteins not present on the surface of H5N1 including the nucleoprotein, the nucleocapsid structural protein, polymerases (PA, PB and PB2), and non-structural proteins (NS1 and NS2). The nucleotide and/or amino acid sequence of proteins of various H5N1 strains can be found in the GenBank-database, NCBI Influenza Virus Sequence Database, Influenza Sequence Database (ISD), EMBL-database and/or other databases. It is well within the reach of the skilled person to find such sequences in the respective databases.

In another embodiment the binding molecules of the invention are capable of specifically binding to a fragment of the above-mentioned proteins and/or polypeptides, wherein the fragment at least comprises an antigenic determinant recognized by the binding molecules of the invention. An "antigenic determinant" as used herein is a moiety that is capable of binding to a binding molecule of the invention with sufficiently high affinity to form a detectable antigen-binding molecule complex. The binding molecules of the invention may or may not be capable of specifically binding to the extracellular part of HA (also called herein soluble HA (sHA)).

The binding molecules of the invention can be intact immunoglobulin molecules such as polyclonal or monoclonal antibodies or the binding molecules can be antigen-binding fragments including, but not limited to, Fab, F(ab'), $F(ab')_2$, Fv, dAb, Fd, complementarity determining region (CDR) fragments, single-chain antibodies (scFv), bivalent single-chain antibodies, single-chain phage antibodies, diabodies, triabodies, tetrabodies, and (poly)peptides that contain at least a fragment of an immunoglobulin that is sufficient to confer specific antigen binding to influenza virus H5N1 strains or a fragment thereof. In a preferred embodiment the binding molecules of the invention are human monoclonal antibodies.

The binding molecules of the invention can be used in non-isolated or isolated form. Furthermore, the binding molecules of the invention can be used alone or in a mixture comprising at least one binding molecule (or variant or fragment thereof) of the invention. In

other words, the binding molecules can be used in combination, *e.g.*, as a pharmaceutical composition comprising two or more binding molecules of the invention, variants or fragments thereof. For example, binding molecules having different, but complementary activities can be combined in a single therapy to achieve a desired prophylactic, therapeutic or diagnostic effect, but alternatively, binding molecules having identical activities can also be combined in a single therapy to achieve a desired prophylactic, therapeutic or diagnostic effect. Optionally, the mixture further comprises at least one other therapeutic agent. Preferably, the therapeutic agent such as, *e.g.*, M2 inhibitors (*e.g.*, amantidine, rimantadine) and/or neuraminidase inhibitors (*e.g.*, zanamivir, oseltamivir) is useful in the prophylaxis and/or treatment of an influenza virus H5N1 infection.

Typically, binding molecules according to the invention can bind to their binding partners, *i.e.* influenza virus H5N1 or fragments thereof, with an affinity constant (K_d-value) that is lower than $0.2x10^{-4}$ M, $1.0x10^{-5}$ M, $1.0x10^{-6}$ M, $1.0x10^{-7}$ M, preferably lower than $1.0x10^{-8}$ M, more preferably lower than $1.0x10^{-9}$ M, more preferably lower than $1.0x10^{-10}$ M, even more preferably lower than $1.0x10^{-11}$ M, and in particular lower than $1.0x10^{-12}$ M. The affinity constants can vary for antibody isotypes. For example, affinity binding for an IgM isotype refers to a binding affinity of at least about $1.0x10^{-7}$ M. Affinity constants can for instance be measured using surface plasmon resonance, for example using the BIACORE system (Pharmacia Biosensor AB, Uppsala, Sweden).

The binding molecules according to the invention may bind to influenza virus H5N1 or a fragment thereof in soluble form such as for instance in a sample or in suspension or may bind to influenza virus H5N1 or a fragment thereof bound or attached to a carrier or substrate, *e.g.*, microtiter plates, membranes and beads, etc. Carriers or substrates may be made of glass, plastic (*e.g.*, polystyrene), polysaccharides, nylon, nitrocellulose, or Teflon, etc. The surface of such supports may be solid or porous and of any convenient shape. Furthermore, the binding molecules may bind to influenza virus H5N1 in purified/isolated or non-purified/non-isolated form.

The binding molecules of the invention exhibit neutralizing activity. Neutralizing activity can for instance be measured as described herein. Alternative assays measuring neutralizing activity are described in for instance WHO Manual on Animal Influenza Diagnosis and Surveillance, Geneva: World Health Organisation, 2005, version 2002.5.

The present invention relates to an isolated human binding molecule that is able to recognize and bind to an epitope in the HA2 subunit of the influenza haemagglutinin protein (HA), characterized in that said binding molecule has neutralizing activity against an influenza virus comprising HA of the H5 subtype. Examples of influenza strains that contain such a HA of the H5 subtype and that are important strains in view of pandemic threats are H5N1, H5N2, H5N8, and H5N9. Particularly preferred are binding molecules that at least neutralize the H5N1 influenza strain. Preferably, said binding molecule according to the invention does not depend on an epitope in the HA1 subunit of the HA protein for binding to said HA protein. The known murine antibody that was described in the art (C179) that also binds to the same epitope in the HA2 domain also depends on binding to an epitope in the HA1 domain of the HA protein. This is disadvantageous as it adds to the possibility of escape mutants that are no longer recognized by the antibody. Moreoever, a number of the antibodies of the present invention (such as CR6307 and CR6323) do not depend on conformational epitopes and recognize the HA2 epitope even in a reduced form (when used in western-blotting). This is an advantage over the antibodies from the art because when a conformational change is induced in the HA protein due to whatever mutation in another part of the protein, such conformational change will not most likely hamper the binding of the antibodies of the present invention to the HA2 epitope, whereas antibodies that do depend on conformation might very well be unable to bind when such mutations occur.

In another preferred embodiment, the binding molecule according to the invention also has neutralizing activity against an influenza virus comprising HA of the H1 subtype, and preferably wherein said binding molecule also has neutralizing activity against an influenza virus comprising HA of the H2, H6 and/or H9 subtype. It has been shown herein that the binding molecules of the present invention interact with an epitope present in the HA2 epitopes present in the H5, H1, H2, H6, and H9 subtypes, and it has been shown that the binding molecules of the present invention cross-neutralize between influenza subtypes because of this epitope-sharing. It is concluded that the binding molecules of the present invention that depend on binding to that particular part in the HA2 domain (and not on another –mutational prone– epitope in HA1) can cross-neutralize between influenza virus subtypes as they do not appear to depend on binding to domains within HA1, which may be

altered significantly due to antigenic drifts. The skilled person, based on what has been disclosed herein, can now determine whether an antibody indeed cross-reacts with HA proteins from different subtypes and also determine whether they are able to neutralize influenza viruses of different subtypes in vivo.

In another preferred aspect of the invention the binding molecule of the present invention binds to an epitope in the HA2 subunit that is selected from the group consisting of amino acid sequence: GVTNKVNSIIDK (SEQ ID NO:368), GVTNKVNSIINK (SEQ ID NO:369), GVTNKENSIIDK (SEQ ID NO:370), GVTNKVNRIIDK (SEQ ID NO:371), GITNKVNSVIEK (SEQ ID NO:372), GITNKENSVIEK (SEQ ID NO:373), GITNKVNSIIDK (SEQ ID NO:374), and KITSKVNNIVDK (SEQ ID NO:375). As can be concluded from the data shown in Table 13, certain binding molecules of the present invention, CR6261, CR6325, and CR6329 interact with the GVTNKVNSIIDK (SEQ ID NO:368) epitope present in H5N1, and are not hampered by a mutation in the TGLRN epitope in HA1 that do influence the binding of C179. Moreover, some binding molecules, such as CR6307 and CR6323 are not even hampered by a escape mutant, as disclosed in Okuno et al. (1993) with a valine -> glutamic acid mutation at position 6 (exemplified by GVTNKENSIIDK (SEQ ID NO:370)). This epitope is part of an extended alpha helix in the HA2 region. The residues in this putative epitope that are predicted to be most solvent exposed are underlined in bold: GVTNKENSIIDK (SEQ ID NO:370). These amino acids would be most accessible to a binding molecule and thus may form the most important region of the epitope. Consistent with this notion the highlighted ammino acids are absolutly conserved in identity and position in all the sequences presented. This knowledge could be used to predict binding epitopes in influenza subtypes that do not carry the same sequence as above (i.e. H3, H7 and B strains).

Preferred is a binding molecule according to the present invention that is selected from the group consisting of:

a) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:1, a heavy chain CDR2 region of SEQ ID NO:2, and a heavy chain CDR3 region of SEQ ID NO:3,

b) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:16, a heavy chain CDR2 region of SEQ ID NO:17, and a heavy chain CDR3 region of SEQ ID NO:18,

c) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:1, a heavy chain CDR2 region of SEQ ID NO:22, and a heavy chain CDR3 region of SEQ ID NO:23,

d) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:27, a heavy chain CDR2 region of SEQ ID NO:28, and a heavy chain CDR3 region of SEQ ID NO:29,

e) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:39, a heavy chain CDR2 region of SEQ ID NO:40, and a heavy chain CDR3 region of SEQ ID NO:41,

f) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:45, a heavy chain CDR2 region of SEQ ID NO:46, and a heavy chain CDR3 region of SEQ ID NO:47,

g) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:1, a heavy chain CDR2 region of SEQ ID NO:49, and a heavy chain CDR3 region of SEQ ID NO:50,

h) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:52, a heavy chain CDR2 region of SEQ ID NO:53, and a heavy chain CDR3 region of SEQ ID NO:54,

i) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:262, a heavy chain CDR2 region of SEQ ID NO:263, and a heavy chain CDR3 region of SEQ ID NO:264,

j) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:268, a heavy chain CDR2 region of SEQ ID NO:269, and a heavy chain CDR3 region of SEQ ID NO:270,

k) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:274, a heavy chain CDR2 region of SEQ ID NO:275, and a heavy chain CDR3 region of SEQ ID NO:276,

l) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:280, a heavy chain CDR2 region of SEQ ID NO:281, and a heavy chain CDR3 region of SEQ ID NO:282,

m) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:286, a heavy chain CDR2 region of SEQ ID NO:287, and a heavy chain CDR3 region of SEQ ID NO:288,

n) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:292, a heavy chain CDR2 region of SEQ ID NO:293, and a heavy chain CDR3 region of SEQ ID NO:294,

o) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:304, a heavy chain CDR2 region of SEQ ID NO:305, and a heavy chain CDR3 region of SEQ ID NO:306, and

p) a binding molecule comprising a heavy chain CDR1 region of SEQ ID NO:310, a heavy chain CDR2 region of SEQ ID NO:311, and a heavy chain CDR3 region of SEQ ID NO:312.

In a preferred embodiment, the binding molecule according to the invention is for a use as a medicament and preferably for the diagnostic, therapeutic and/or prophylactic

treatment of influenza infection. In one aspect of such use, said influenza infection is caused by an influenza virus that is associated with a pandemic outbreak, or has the potential to be associated with a pandemic outbreak (see WO 2007/045674 and the tables therein). Preferably, the influenza virus strain that is associated with a pandemic outbreak and wherein the disease caused by these strains can be treated by the binding molecules of the present invention, is selected from the group consisting of H1N1, H5N1, H5N2, H5N8, H5N9, H2-based viruses, and H9N2.

The present invention also relates to a pharmaceutical composition comprising a binding molecule according to the invention, and a pharmaceutically acceptable excipient.

In yet another embodiment the invention relates to a use of a binding molecule according to the invention in the preparation of a medicament for the diagnosis, prophylaxis, and/or treatment of an influenza virus infection. Such infections can occur in small populations, but can also spread around the world in seasonal epidemics or, worse, in global pandemics where millions of individuals are at risk. The invention provides binding molecules that can neutralize the infection of influenza strains that cause such seasonal epidemics as well as potential pandemics. Importantly, protection and treatment can be envisioned now with the binding molecules of the present invention in relation to multiple influenza strains as it has been disclosed that due to the binding of an epitope that is shared between HA proteins of different influenza strains, cross-neutralization between such strains is now possible by using the binding molecules of the present invention. This is highly advantageous as the binding molecules can protect mammals when they are administered either before or after infection (as disclosed in the examples), and therefore also when it is unclear (in early stages of occurrence) whether the infection is caused by an H1, an H2, an H5, an H6 or an H9-based strain. Health workers, military forces as well as the general population may be treated prophylactically, or treated upon infection, with the binding molecules of the present invention. Potentially, the binding molecules of the present invention can be prepared and stored in huge stocks because it will provide protection against different pandemic strains, and this will be beneficial in the preparedness of possible influenza pandemics in the future.

In a preferred embodiment, the human binding molecules according to the invention are characterized in that the human binding molecules are selected from the group consisting of: a) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:2, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:3, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:4, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:5, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:6, b) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:2, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:3, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:7, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:8, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:9, c) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:2, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:3, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:10, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:11, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:12, d) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ lD NO:2, a heavy chain CDR3 region having the amino acid sequence of SEQ lD NO:3, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:13, a light chain CDR2 region having the amino acid sequence of SEQ lD NO:14, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:15, e) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:16, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:17, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:18, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:19, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:20, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:21, f) a human binding molecule comprising a heavy chain CDR1

region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:22, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:23, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:24, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:25, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:26, g) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:27, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:28, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:29, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:30, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:31, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:32, h) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:2, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:3, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:33, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:34, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:35, i) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:2, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:3, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:36, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:37, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:38, j) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:39, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:40, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:41, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:42, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:43, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:44, k) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:45, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:46, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:47, a

light chain CDR1 region having the amino acid sequence of SEQ ID NO:7, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:8, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:48, l) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:49, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:50, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:33, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:34, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:51, m) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:52, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:53, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:54, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:55, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:56, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:57, n) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:262, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:263, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:264, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:265, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:266, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:267, o) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:268, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:269, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:270, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:271, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:272, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:273, p) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:274, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:275, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:276, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:277, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:278, and a light chain CDR3 region having the amino acid

sequence of SEQ ID NO:279, q) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:280, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:281, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:282, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:283, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:284, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:285, r) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:286, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:287, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:288, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:289, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:290, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:291, s) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:292, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:293, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:294, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:295, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:296, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:297, t) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:304, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:305, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:306, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:307, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:308, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:309, u) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:310, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:311, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:312, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:313, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:314, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:315, v) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:238, a heavy chain CDR2 region having the

amino acid sequence of SEQ ID NO:239, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:240, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:241, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:242, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:243, w) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:244, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:245, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:246, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:247, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:248, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:249, x) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:250, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:251, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:252, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:253, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:254, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:255, y) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:256, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:257, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:258, a light chain CDR1 region having the amino acid sequence of SEQ lD NO:259, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:260, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:261, and z) a human binding molecule comprising a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:298, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:299, a heavy chain CDR3 region having the amino acid sequence of SEQ ID NO:300, a light chain CDR1 region having the amino acid sequence of SEQ ID NO:301, a light chain CDR2 region having the amino acid sequence of SEQ ID NO:302, and a light chain CDR3 region having the amino acid sequence of SEQ ID NO:303.

In a specific embodiment the binding molecules of the invention comprise a heavy chain CDR1 region having the amino acid sequence of SEQ ID NO:1, a heavy chain CDR2 region having the amino acid sequence of SEQ ID NO:2, and a heavy chain CDR3 region

having the amino acid sequence of SEQ ID NO:3. The CDR regions of the binding molecules of the invention are shown in Table 7. CDR regions are according to Kabat *et al.* (1991) as described in Sequences of Proteins of Immunological Interest. In an embodiment of th epresent invention binding molecules may comprise two, three, four, five or all six CDR regions as disclosed herein. Preferably, a binding molecule according to the present invention comprises at least two of the CDRs disclosed herein.

In an embodiment the binding molecules of the invention comprise the VH germline VH1-69 (see Tomlinson IM, Williams SC, Ignatovitch O, Corbett SJ, Winter G. V-BASE Sequence Directory. Cambridge United Kingdom: MRC Centre for Protein Engineering (1997)). In yet another embodiment, the binding molecules according to the invention comprise a heavy chain comprising the variable heavy chain of the amino acid sequence selected from the group consisting of SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:63, SEQ ID NO:65, SEQ ID NO:67, SEQ ID NO:69, SEQ ID NO:71, SEQ ID NO:73, SEQ ID NO:75, SEQ ID NO:77, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:83, SEQ ID NO:317, SEQ ID NO:321, SEQ ID NO:325, SEQ ID NO:329, SEQ ID NO:333, SEQ ID NO:337, SEQ ID NO:341, SEQ ID NO:345, SEQ ID NO:349, SEQ ID NO:353, SEQ ID NO:357, SEQ ID NO:361, and SEQ ID NO:365. In a further embodiment, the binding molecules according to the invention comprise a light chain comprising the variable light chain of the amino acid sequence selected from the group consisting of SEQ ID NO:85, SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, SEQ ID NO:107, SEQ ID NO:109, SEQ ID NO:319, SEQ ID NO:323, SEQ ID NO:327, SEQ ID NO:331, SEQ ID NO:335, SEQ ID NO:339, SEQ ID NO:343, SEQ ID NO:347, SEQ ID NO:351, SEQ ID NO:355, SEQ ID NO:359, SEQ ID NO:363, and SEQ ID NO:367. Table 8 specifies the heavy and light chain variable regions of the binding molecule of the invention.

Another aspect of the invention includes functional variants of the binding molecules as defined herein. Molecules are considered to be functional variants of a binding molecule according to the invention, if the variants are capable of competing for specifically binding to influenza virus H5N1 or a fragment thereof with the parental binding molecules. In other words, when the functional variants are still capable of binding to influenza virus H5N1 or a fragment thereof. Preferably, the functional variants are capable of competing for specifically

binding to at least two (or more) different influenza virus H5N1 strains or fragments thereof that are specifically bound by the parental binding molecules. Furthermore, molecules are considered to be functional variants of a binding molecule according to the invention, if they have neutralizing activity against influenza virus H5N1, preferably against the at least two (or more) influenza virus H5N1 strains against which the parental binding molecule exhibits neutralizing activity. Functional variants include, but are not limited to, derivatives that are substantially similar in primary structural sequence, but which contain *e.g. in vitro* or *in vivo* modifications, chemical and/or biochemical, that are not found in the parental binding molecule. Such modifications include *inter alia* acetylation, acylation, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, cross-linking, disulfide bond formation, glycosylation, hydroxylation, methylation, oxidation, pegylation, proteolytic processing, phosphorylation, and the like.

Alternatively, functional variants can be binding molecules as defined in the present invention comprising an amino acid sequence containing substitutions, insertions, deletions or combinations thereof of one or more amino acids compared to the amino acid sequences of the parental binding molecules. Furthermore, functional variants can comprise truncations of the amino acid sequence at either or both the amino or carboxyl termini. Functional variants according to the invention may have the same or different, either higher or lower, binding affinities compared to the parental binding molecule but are still capable of binding to influenza virus H5N1 or a fragment thereof. For instance, functional variants according to the invention may have increased or decreased binding affinities for influenza virus H5N1 or a fragment thereof compared to the parental binding molecules. Preferably, the amino acid sequences of the variable regions, including, but not limited to, framework regions, hypervariable regions, in particular the CDR3 regions, are modified. Generally, the light chain and the heavy chain variable regions comprise three hypervariable regions, comprising three CDRs, and more conserved regions, the so-called framework regions (FRs). The hypervariable regions comprise amino acid residues from CDRs and amino acid residues from hypervariable loops. Functional variants intended to fall within the scope of the present invention have at least about 50% to about 99%, preferably at least about 60% to about 99%, more preferably at least about 70% to about 99%, even more preferably at least about 80% to about 99%, most preferably at least about 90% to about 99%, in particular at least about 95%

to about 99%, and in particular at least about 97% to about 99% amino acid sequence homology with the parental binding molecules as defined herein. Computer algorithms such as *inter alia* Gap or Bestfit known to a person skilled in the art can be used to optimally align amino acid sequences to be compared and to define similar or identical amino acid residues. Functional variants can be obtained by altering the parental binding molecules or parts thereof by general molecular biology methods known in the art including, but not limited to, error-prone PCR, oligonucleotide-directed mutagenesis, site-directed mutagenesis and heavy and/or light chain shuffling. In an embodiment the functional variants of the invention have neutralizing activity against influenza virus H5N1. The neutralizing activity may either be identical, or be higher or lower compared to the parental binding molecules. Henceforth, when the term (human) binding molecule is used, this also encompasses functional variants of the (human) binding molecule.

In yet a further aspect, the invention includes immunoconjugates, *i.e.* molecules comprising at least one binding molecule as defined herein and further comprising at least one tag, such as *inter alia* a detectable moiety/agent. Also contemplated in the present invention are mixtures of immunoconjugates according to the invention or mixtures of at least one immunoconjugates according to the invention and another molecule, such as a therapeutic agent or another binding molecule or immunoconjugate. In a further embodiment, the immunoconjugates of the invention may comprise more than one tag. These tags can be the same or distinct from each other and can be joined/conjugated non-covalently to the binding molecules. The tag(s) can also be joined/conjugated directly to the human binding molecules through covalent bonding. Alternatively, the tag(s) can be joined/conjugated to the binding molecules by means of one or more linking compounds. Techniques for conjugating tags to binding molecules are well known to the skilled artisan.

The tags of the immunoconjugates of the present invention may be therapeutic agents, but they can also be detectable moieties/agents. Tags suitable in therapy and/or prevention may be toxins or functional parts thereof, antibiotics, enzymes, other binding molecules that enhance phagocytosis or immune stimulation. Immunoconjugates comprising a detectable agent can be used diagnostically to, for example, assess if a subject has been infected with an influenza virus H5N1 strain or monitor the development or progression of an influenza virus H5N1 infection as part of a clinical testing procedure to, *e.g.*, determine the efficacy of a

given treatment regimen. However, they may also be used for other detection and/or analytical and/or diagnostic purposes. Detectable moieties/agents include, but are not limited to, enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals, and non-radioactive paramagnetic metal ions. The tags used to label the binding molecules for detection and/or analytical and/or diagnostic purposes depend on the specific detection/analysis/diagnosis techniques and/or methods used such as *inter alia* immunohistochemical staining of (tissue) samples, flow cytometric detection, scanning laser cytometric detection, fluorescent immunoassays, enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), bioassays (*e.g.*, phagocytosis assays), Western blotting applications, etc. Suitable labels for the detection/analysis/diagnosis techniques and/or methods known in the art are well within the reach of the skilled artisan.

Furthermore, the human binding molecules or immunoconjugates of the invention can also be attached to solid supports, which are particularly useful for *in vitro* immunoassays or purification of influenza virus H5N1 or a fragment thereof. Such solid supports might be porous or nonporous, planar or non-planar. The binding molecules of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. Examples include, but are not limited to, the hexa-histidine tag, the hemagglutinin (HA) tag, the myc tag or the flag tag. Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate. In another aspect the binding molecules of the invention may be conjugated/attached to one or more antigens. Preferably, these antigens are antigens which are recognized by the immune system of a subject to which the binding molecule-antigen conjugate is administered. The antigens may be identical, but may also differ from each other. Conjugation methods for attaching the antigens and binding molecules are well known in the art and include, but are not limited to, the use of cross-linking agents. The binding molecules of the invention will bind to influenza virus H5N1 and the antigens attached to the binding molecules will initiate a powerful T-cell attack on the conjugate, which will eventually lead to the destruction of the influenza virus H5N1.

Next to producing immunoconjugates chemically by conjugating, directly or indirectly, via for instance a linker, the immunoconjugates can be produced as fusion proteins comprising the binding molecules of the invention and a suitable tag. Fusion proteins can be

produced by methods known in the art such as, *e.g.*, recombinantly by constructing nucleic acid molecules comprising nucleotide sequences encoding the binding molecules in frame with nucleotide sequences encoding the suitable tag(s) and then expressing the nucleic acid molecules.

It is another aspect of the present invention to provide a nucleic acid molecule encoding at least a binding molecule, functional variant or immunoconjugate according to the invention. Such nucleic acid molecules can be used as intermediates for cloning purposes, *e.g.* in the process of affinity maturation as described above. In a preferred embodiment, the nucleic acid molecules are isolated or purified.

The skilled man will appreciate that functional variants of these nucleic acid molecules are also intended to be a part of the present invention. Functional variants are nucleic acid sequences that can be directly translated, using the standard genetic code, to provide an amino acid sequence identical to that translated from the parental nucleic acid molecules.

Preferably, the nucleic acid molecules encode binding molecules comprising the CDR regions as described above. In a further embodiment the nucleic acid molecules encode binding molecules comprising two, three, four, five or even all six CDR regions of the binding molecules of the invention.

In another embodiment, the nucleic acid molecules encode binding molecules comprising a heavy chain comprising the variable heavy chain sequences as described above. In another embodiment the nucleic acid molecules encode binding molecules comprising a light chain comprising the variable light chain sequences as described above. The nucleotide sequences of the binding molecules of the invention are given in the Example section (see, *e.g.*, Tables 6 and 8).

It is another aspect of the invention to provide vectors, *i.e.* nucleic acid constructs, comprising one or more nucleic acid molecules according to the present invention. Vectors can be derived from plasmids such as *inter alia* F, R1, RP1, Col, pBR322, TOL, Ti, etc; cosmids; phages such as lambda, lambdoid, M13, Mu, P1, P22, Qβ, T-even, T-odd, T2, T4, T7, etc; plant viruses. Vectors can be used for cloning and/or for expression of the binding molecules of the invention and might even be used for gene therapy purposes. Vectors comprising one or more nucleic acid molecules according to the invention operably linked to

one or more expression-regulating nucleic acid molecules are also covered by the present invention. The choice of the vector is dependent on the recombinant procedures followed and the host used. Introduction of vectors in host cells can be effected by *inter alia* calcium phosphate transfection, virus infection, DEAE-dextran mediated transfection, lipofectamin transfection or electroporation. Vectors may be autonomously replicating or may replicate together with the chromosome into which they have been integrated. Preferably, the vectors contain one or more selection markers. The choice of the markers may depend on the host cells of choice, although this is not critical to the invention as is well known to persons skilled in the art. They include, but are not limited to, kanamycin, neomycin, puromycin, hygromycin, zeocin, thymidine kinase gene from Herpes simplex virus (HSV-TK), dihydrofolate reductase gene from mouse (dhfr). Vectors comprising one or more nucleic acid molecules encoding the human binding molecules as described above operably linked to one or more nucleic acid molecules encoding proteins or peptides that can be used to isolate the human binding molecules are also covered by the invention. These proteins or peptides include, but are not limited to, glutathione-S-transferase, maltose binding protein, metal-binding polyhistidine, green fluorescent protein, luciferase and beta-galactosidase.

Hosts containing one or more copies of the vectors mentioned above are an additional subject of the present invention. Preferably, the hosts are host cells. Host cells include, but are not limited to, cells of mammalian, plant, insect, fungal or bacterial origin. Bacterial cells include, but are not limited to, cells from Gram-positive bacteria or Gram-negative bacteria such as several species of the genera *Escherichia*, such as *E. coli*, and *Pseudomonas*. In the group of fungal cells preferably yeast cells are used. Expression in yeast can be achieved by using yeast strains such as *inter alia Pichia pastoris*, *Saccharomyces cerevisiae* and *Hansenula polymorpha*. Furthermore, insect cells such as cells from Drosophila and Sf9 can be used as host cells. Besides that, the host cells can be plant cells such as *inter alia* cells from crop plants such as forestry plants, or cells from plants providing food and raw materials such as cereal plants, or medicinal plants, or cells from ornamentals, or cells from flower bulb crops. Transformed (transgenic) plants or plant cells are produced by known methods, for example, Agrobacterium-mediated gene transfer, transformation of leaf discs, protoplast transformation by polyethylene glycol-induced DNA transfer, electroporation, sonication, microinjection or bolistic gene transfer. Additionally, a suitable expression system can be a

baculovirus system. Expression systems using mammalian cells such as Chinese Hamster Ovary (CHO) cells, COS cells, BHK cells, NSO cells or Bowes melanoma cells are preferred in the present invention. Mammalian cells provide expressed proteins with posttranslational modifications that are most similar to natural molecules of mammalian origin. Since the present invention deals with molecules that may have to be administered to humans, a completely human expression system would be particularly preferred. Therefore, even more preferably, the host cells are human cells. Examples of human cells are *inter alia* HeLa, 911, AT1080, A549, 293 and HEK293T cells. In preferred embodiments, the human producer cells comprise at least a functional part of a nucleic acid sequence encoding an adenovirus E1 region in expressible format. In even more preferred embodiments, said host cells are derived from a human retina and immortalized with nucleic acids comprising adenoviral E1 sequences, such as 911 cells or the cell line deposited at the European Collection of Cell Cultures (ECACC), CAMR, Salisbury, Wiltshire SP4 OJG, Great Britain on 29 February 1996 under number 96022940 and marketed under the trademark PER.C6® (PER.C6 is a registered trademark of Crucell Holland B.V.). For the purposes of this application "PER.C6 cells" refers to cells deposited under number 96022940 or ancestors, passages up-stream or downstream as well as descendants from ancestors of deposited cells, as well as derivatives of any of the foregoing. Production of recombinant proteins in host cells can be performed according to methods well known in the art. The use of the cells marketed under the trademark PER.C6® as a production platform for proteins of interest has been described in WO 00/63403 the disclosure of which is incorporated herein by reference in its entirety.

A method of producing a binding molecule according to the invention is an additional part of the invention. The method comprises the steps of a) culturing a host according to the invention under conditions conducive to the expression of the binding molecule, and b) optionally, recovering the expressed binding molecule. The expressed binding molecules can be recovered from the cell free extract, but preferably they are recovered from the culture medium. The above method of producing can also be used to make functional variants of the binding molecules and/or immunoconjugates of the present invention. Methods to recover proteins, such as binding molecules, from cell free extracts or culture medium are well known to the man skilled in the art. Binding molecules, functional variants and/or immunoconjugates as obtainable by the above-described method are also a part of the present invention.

Alternatively, next to the expression in hosts, such as host cells, the binding molecules and immunoconjugates of the invention can be produced synthetically by conventional peptide synthesizers or in cell-free translation systems using RNA nucleic acid derived from DNA molecules according to the invention. Binding molecules and immunoconjugates as obtainable by the above described synthetic production methods or cell-free translation systems are also a part of the present invention.

In yet another embodiment, binding molecules of the present invention can also be produced in transgenic, non-human, mammals such as *inter alia* rabbits, goats or cows, and secreted into for instance the milk thereof.

In yet another alternative embodiment, binding molecules according to the present invention, preferably human binding molecules specifically binding to influenza virus H5N1 or a fragment thereof, may be generated by transgenic non-human mammals, such as for instance transgenic mice or rabbits, that express human immunoglobulin genes. Preferably, the transgenic non-human mammals have a genome comprising a human heavy chain transgene and a human light chain transgene encoding all or a portion of the human binding molecules as described above. The transgenic non-human mammals can be immunized with a purified or enriched preparation of influenza virus H5N1 or a fragment thereof. Protocols for immunizing non-human mammals are well established in the art. See Using Antibodies: A Laboratory Manual, Edited by: E. Harlow, D. Lane (1998), Cold Spring Harbor Laboratory, Cold Spring Harbor, New York and Current Protocols in Immunology, Edited by: J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W. Strober (2001), John Wiley & Sons Inc., New York, the disclosures of which are incorporated herein by reference. Immunization protocols often include multiple immunizations, either with or without adjuvants such as Freund's complete adjuvant and Freund's incomplete adjuvant, but may also include naked DNA immunizations. In another embodiment, the human binding molecules are produced by B-cells, plasma and/or memory cells derived from the transgenic animals. In yet another embodiment, the human binding molecules are produced by hybridomas, which are prepared by fusion of B-cells obtained from the above-described transgenic non-human mammals to immortalized cells. B-cells, plasma cells and hybridomas as obtainable from the above-described transgenic non-human mammals and human binding molecules as obtainable

from the above-described transgenic non-human mammals, B-cells, plasma and/or memory cells and hybridomas are also a part of the present invention.

In a further aspect, the invention provides a method of identifying a binding molecule, such as a human binding molecule, *e.g.* a human monoclonal antibody or fragment thereof, specifically binding to influenza virus H5N1 or nucleic acid molecules encoding such binding molecules and comprises the steps of: (a) contacting a collection of binding molecules on the surface of replicable genetic packages with influenza virus H5N1 or a fragment thereof under conditions conducive to binding, (b) selecting at least once for a replicable genetic package binding to influenza virus H5N1 or a fragment thereof, (c) separating and recovering the replicable genetic package binding to influenza virus H5N1 or a fragment thereof from replicable genetic packages that do not bind to influenza virus H5N1 or a fragment thereof. A replicable genetic package as used herein can be prokaryotic or eukaryotic and includes cells, spores, yeasts, bacteria, viruses, (bacterio)phage, ribosomes and polysomes. A preferred replicable genetic package is a phage. The binding molecules, such as for instance single chain Fvs, are displayed on the replicable genetic package, *i.e.* they are attached to a group or molecule located at an exterior surface of the replicable genetic package. The replicable genetic package is a screenable unit comprising a binding molecule to be screened linked to a nucleic acid molecule encoding the binding molecule. The nucleic acid molecule should be replicable either *in vivo* (*e.g.*, as a vector) or *in vitro* (*e.g.*, by PCR, transcription and translation). *In vivo* replication can be autonomous (as for a cell), with the assistance of host factors (as for a virus) or with the assistance of both host and helper virus (as for a phagemid). Replicable genetic packages displaying a collection of binding molecules is formed by introducing nucleic acid molecules encoding exogenous binding molecules to be displayed into the genomes of the replicable genetic packages to form fusion proteins with endogenous proteins that are normally expressed from the outer surface of the replicable genetic packages. Expression of the fusion proteins, transport to the outer surface and assembly results in display of exogenous binding molecules from the outer surface of the replicable genetic packages.

The selection step(s) in the method according to the present invention can be performed with influenza H5N1 viruses that are live and still infective or inactivated. Inactivation of influenza virus H5N1 may be performed by viral inactivation methods well

known to the skilled artisan such as *inter alia* treatment with formalin, β-propiolactone (BPL), merthiolate, and/or ultraviolet light. Methods to test, if influenza virus H5N1 is still alive, infective and/or viable or partly or completely inactivated are well known to the person skilled in the art. The influenza virus H5N1 used in the above method may be non-isolated, *e.g.* present in serum and/or blood of an infected individual. The influenza virus H5N1 used may also be isolated from cell culture in a suitable medium.

In an embodiment the influenza virus H5N1 is in suspension when contacted with the replicable genetic packages. Alternatively, they may also be coupled to a carrier when contact takes place. In an embodiment a first and further selection may take place against an influenza virus H5N1 strain of the same clade. Alternatively, first and further selection rounds may be performed against influenza virus H5N1 strains of different clades (*e.g.* first selection on clade 1 strains and second selection on clade 2 or 3 strains).

Alternatively, the selection step(s) may be performed in the presence of a fragment of influenza virus H5N1 such as *e.g.* cell membrane preparations, recombinant H5N1 proteins or polypeptides, fusion proteins comprising H5N1 proteins or polypeptides, cells expressing recombinant H5N1 proteins or polypeptides, and the like. Extracellularly exposed parts of these proteins or polypeptides can also be used as selection material. The fragments of influenza virus H5N1 may be immobilized to a suitable material before use or may be used in suspension. In an embodiment the selection can be performed on different fragments of influenza virus H5N1 or fragments of different influenza virus H5N1 strains. Finding suitable selection combinations are well within the reach of the skilled artisan. Selections may be performed by ELISA or FACS.

In yet a further aspect, the invention provides a method of obtaining a binding molecule specifically binding to an influenza virus H5N1 strain or fragment thereof or a nucleic acid molecule encoding such a binding molecule, wherein the method comprises the steps of a) performing the above described method of identifying binding molecules, and b) isolating from the recovered replicable genetic package the binding molecule and/or the nucleic acid molecule encoding the binding molecule. The collection of binding molecules on the surface of replicable genetic packages can be a collection of scFvs or Fabs. Once a new scFv or Fab has been established or identified with the above-mentioned method of identifying binding molecules or nucleic acid molecules encoding the binding molecules, the

DNA encoding the scFv or Fab can be isolated from the bacteria or phages and combined with standard molecular biological techniques to make constructs encoding scFvs, bivalent scFvs, Fabs or complete human immunoglobulins of a desired specificity (*e.g.* IgG, IgA or IgM). These constructs can be transfected into suitable cell lines and complete human monoclonal antibodies can eventually be produced (see Huls *et al.,* 1999; Boel *et al.*, 2000).

As mentioned before the preferred replicable genetic package is a phage. Phage display methods for identifying and obtaining (human) binding molecules, *e.g.* (human) monoclonal antibodies, are by now well-established methods known by the person skilled in the art. They are, *e.g.*, described in US Patent Number 5,696,108; Burton and Barbas, 1994; de Kruif *et al.*, 1995b; and Phage Display: A Laboratory Manual. Edited by: CF Barbas, DR Burton, JK Scott and GJ Silverman (2001), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. All these references are herewith incorporated herein in their entirety. For the construction of phage display libraries, collections of human monoclonal antibody heavy and light chain variable region genes are expressed on the surface of bacteriophage, preferably filamentous bacteriophage, particles, in for example single-chain Fv (scFv) or in Fab format (see de Kruif *et al.*, 1995b). Large libraries of antibody fragment-expressing phages typically contain more than $1.0x10^9$ antibody specificities and may be assembled from the immunoglobulin V-regions expressed in the B-lymphocytes of immunized- or non-immunized individuals. In a specific embodiment of the invention the phage library of binding molecules, preferably scFv phage library, is prepared from RNA isolated from cells obtained from a subject that has been vaccinated against influenza virus (*e.g.*, H5N1), recently vaccinated against an unrelated pathogen, recently suffered from a influenza virus H5N1 infection or from a healthy individual. RNA can be isolated from *inter alia* bone marrow or peripheral blood, preferably peripheral blood lymphocytes or isolated B-cells or even subpopulations of B-cells such as memory B-cells. The subject can be an animal, preferably a human. In a preferred embodiment the libraries may be assembled from the immunoglobulin V-regions expressed by IgM memory B-cells.

Alternatively, phage display libraries may be constructed from immunoglobulin variable regions that have been partially assembled *in vitro* to introduce additional antibody diversity in the library (semi-synthetic libraries). For example, *in vitro* assembled variable regions contain stretches of synthetically produced, randomized or partially randomized DNA

in those regions of the molecules that are important for antibody specificity, *e.g.* CDR regions. Phage antibodies specific for influenza virus H5N1 can be selected from the library by exposing the virus or fragment thereof to a phage library to allow binding of phages expressing antibody fragments specific for the virus or fragment thereof. Non-bound phages are removed by washing and bound phages eluted for infection of *E.coli* bacteria and subsequent propagation. Multiple rounds of selection and propagation are usually required to sufficiently enrich for phages binding specifically to the virus or fragment thereof. If desired, before exposing the phage library to the virus or fragment thereof the phage library can first be subtracted by exposing the phage library to non-target material such as viruses or fragments thereof of a different strain, *i.e.* non-H5N1 influenza viruses. These subtractor viruses or fragments thereof can be bound to a solid phase or can be in suspension. Phages may also be selected for binding to complex antigens such as complex mixtures of H5N1 proteins or (poly)peptides optionally supplemented with other material. Host cells expressing one or more proteins or (poly)peptides of influenza virus H5N1 may also be used for selection purposes. A phage display method using these host cells can be extended and improved by subtracting non-relevant binders during screening by addition of an excess of host cells comprising no target molecules or non-target molecules that are similar, but not identical, to the target, and thereby strongly enhance the chance of finding relevant binding molecules. Of course, the subtraction may be performed before, during or after the screening with virus or fragments thereof. The process is referred to as the MABSTRACT® process (MABSTRACT® is a registered trademark of Crucell Holland B.V., see also US Patent Number 6,265,150 which is incorporated herein by reference).

In yet another aspect the invention provides a method of obtaining a binding molecule potentially having neutralizing activity against influenza virus H5N1, preferably at least against influenza virus H5N1 strains of clade 1, clade 2 and clade 3, wherein the method comprises the steps of (a) performing the method of obtaining a binding molecule specifically binding to influenza virus H5N1 or a fragment thereof or a nucleic acid molecule encoding such a binding molecule as described above, and (b) verifying if the binding molecule isolated has neutralizing activity against the virus, preferably against at least influenza virus H5N1 strains of clade 1 and clade 2. Assays for verifying if a binding molecule has neutralizing

activity are well known in the art (see WHO Manual on Animal Influenza Diagnosis and Surveillance, Geneva: World Health Organisation, 2005 version 2002.5).

In a further aspect the invention pertains to a binding molecule having neutralizing activity being obtainable by the methods as described above.

In yet a further aspect, the invention provides compositions comprising at least a binding molecule preferably a human monoclonal antibody according to the invention, at least a functional variant thereof, at least an immunoconjugate according to the invention or a combination thereof. In addition to that, the compositions may comprise *inter alia* stabilizing molecules, such as albumin or polyethylene glycol, or salts. Preferably, the salts used are salts that retain the desired biological activity of the binding molecules and do not impart any undesired toxicological effects. If necessary, the human binding molecules of the invention may be coated in or on a material to protect them from the action of acids or other natural or non-natural conditions that may inactivate the binding molecules.

In yet a further aspect, the invention provides compositions comprising at least a nucleic acid molecule as defined in the present invention. The compositions may comprise aqueous solutions such as aqueous solutions containing salts (*e.g.*, NaCl or salts as described above), detergents (*e.g.*, SDS) and/or other suitable components.

Furthermore, the present invention pertains to pharmaceutical compositions comprising at least a binding molecule such as a human monoclonal antibody of the invention (or functional fragment or variant thereof), at least an immunoconjugate according to the invention, at least a composition according to the invention, or combinations thereof. The pharmaceutical composition of the invention further comprises at least one pharmaceutically acceptable excipient. Pharmaceutically acceptable excipients are well known to the skilled person. The pharmaceutical composition according to the invention may further comprise at least one other therapeutic agent. Suitable agents are also well known to the skilled artisan.

In an embodiment the pharmaceutical compositions may comprise two or more binding molecules that have neutralizing activity against influenza virus H5N1. In an embodiment, the binding molecules exhibit synergistic neutralizing activity, when used in combination. In other words, the compositions comprise at least two binding molecules having neutralizing activity, characterized in that the binding molecules act synergistically in neutralizing influenza virus H5N1. As used herein, the term "synergistic" means that the

combined effect of the binding molecules when used in combination is greater than their additive effects when used individually. The synergistically acting binding molecules may bind to different structures on the same or distinct fragments of influenza virus H5N1. A way of calculating synergy is by means of the combination index. The concept of the combination index (CI) has been described by Chou and Talalay (1984). The compositions may also comprise one binding molecule having neutralizing activity and one non-neutralizing H5N1-specific binding molecule. The non-neutralizing and neutralizing H5N1-specific binding molecules may also act synergistically in neutralizing influenza virus H5N1.

A pharmaceutical composition according to the invention can further comprise at least one other therapeutic, prophylactic and/or diagnostic agent. Preferably, the pharmaceutical composition comprises at least one other prophylactic and/or therapeutic agent. Preferably, said further therapeutic and/or prophylactic agents are agents capable of preventing and/or treating an influenza virus H5N1 infection and/or a condition resulting from such an infection. Therapeutic and/or prophylactic agents include, but are not limited to, anti-viral agents. Such agents can be binding molecules, small molecules, organic or inorganic compounds, enzymes, polynucleotide sequences, anti-viral peptides, etc. Other agents that are currently used to treat patients infected with influenza virus H5N1 are M2 inhibitors (*e.g.*, amantidine, rimantadine) and/or neuraminidase inhibitors (*e.g.*, zanamivir, oseltamivir). These can be used in combination with the binding molecules of the invention. Agents capable of preventing and/or treating an infection with influenza virus H5N1 and/or a condition resulting from such an infection that are in the experimental phase might also be used as other therapeutic and/or prophylactic agents useful in the present invention.

The binding molecules or pharmaceutical compositions of the invention can be tested in suitable animal model systems prior to use in humans. Such animal model systems include, but are not limited to, mouse, ferret and monkey.

Typically, pharmaceutical compositions must be sterile and stable under the conditions of manufacture and storage. The binding molecules, immunoconjugates, nucleic acid molecules or compositions of the present invention can be in powder form for reconstitution in the appropriate pharmaceutically acceptable excipient before or at the time of delivery. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying (lyophilization) that

yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Alternatively, the binding molecules, immunoconjugates, nucleic acid molecules or compositions of the present invention can be in solution and the appropriate pharmaceutically acceptable excipient can be added and/or mixed before or at the time of delivery to provide a unit dosage injectable form. Preferably, the pharmaceutically acceptable excipient used in the present invention is suitable to high drug concentration, can maintain proper fluidity and, if necessary, can delay absorption.

The choice of the optimal route of administration of the pharmaceutical compositions will be influenced by several factors including the physico-chemical properties of the active molecules within the compositions, the urgency of the clinical situation and the relationship of the plasma concentrations of the active molecules to the desired therapeutic effect. For instance, if necessary, the binding molecules of the invention can be prepared with carriers that will protect them against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can *inter alia* be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Furthermore, it may be necessary to coat the binding molecules with, or co-administer the binding molecules with, a material or compound that prevents the inactivation of the human binding molecules. For example, the binding molecules may be administered to a subject in an appropriate carrier, for example, liposomes or a diluent.

The routes of administration can be divided into two main categories, oral and parenteral administration. The preferred administration route is intravenous or by inhalation.

Oral dosage forms can be formulated *inter alia* as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard capsules, soft gelatin capsules, syrups or elixirs, pills, dragees, liquids, gels, or slurries. These formulations can contain pharmaceutically excipients including, but not limited to, inert diluents, granulating and disintegrating agents, binding agents, lubricating agents, preservatives, colouring, flavouring or sweetening agents, vegetable or mineral oils, wetting agents, and thickening agents.

The pharmaceutical compositions of the present invention can also be formulated for parenteral administration. Formulations for parenteral administration can be *inter alia* in the form of aqueous or non-aqueous isotonic sterile non-toxic injection or infusion solutions or suspensions. The solutions or suspensions may comprise agents that are non-toxic to recipients at the dosages and concentrations employed such as 1,3-butanediol, Ringer's solution, Hank's solution, isotonic sodium chloride solution, oils, fatty acids, local anaesthetic agents, preservatives, buffers, viscosity or solubility increasing agents, water-soluble antioxidants, oil-soluble antioxidants and metal chelating agents.

In a further aspect, the binding molecules such as human monoclonal antibodies (functional fragments and variants thereof), immunoconjugates, compositions, or pharmaceutical compositions of the invention can be used as a medicament. So, a method of treatment and/or prevention of an influenza virus H5N1 infection using the binding molecules, immunoconjugates, compositions, or pharmaceutical compositions of the invention is another part of the present invention. The above-mentioned molecules can *inter alia* be used in the diagnosis, prophylaxis, treatment, or combination thereof, of an influenza virus H5N1 infection. They are suitable for treatment of yet untreated patients suffering from an influenza virus H5N1 infection and patients who have been or are treated for an influenza virus H5N1 infection. They may be used for patients such as healthcare workers, relatives of infected subjects, (poultry-)farmers, etc.

The above-mentioned molecules or compositions may be employed in conjunction with other molecules useful in diagnosis, prophylaxis and/or treatment. They can be used *in vitro, ex vivo* or *in vivo*. For instance, the binding molecules such as human monoclonal antibodies (or functional variants thereof), immunoconjugates, compositions or pharmaceutical compositions of the invention can be co-administered with a vaccine against influenza virus H5N1 (if available). Alternatively, the vaccine may also be administered before or after administration of the molecules of the invention. Instead of a vaccine, anti-viral agents can also be employed in conjunction with the binding molecules of the present invention. Suitable anti-viral agents are mentioned above.

The molecules are typically formulated in the compositions and pharmaceutical compositions of the invention in a therapeutically or diagnostically effective amount. Alternatively, they may be formulated and administered separately. For instance the other

molecules such as the anti-viral agents may be applied systemically, while the binding molecules of the invention may be applied intravenously.

Dosage regimens can be adjusted to provide the optimum desired response (*e.g.*, a therapeutic response). A suitable dosage range may for instance be 0.1-100 mg/kg body weight, preferably 0.5-15 mg/kg body weight. Furthermore, for example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. The molecules and compositions according to the present invention are preferably sterile. Methods to render these molecules and compositions sterile are well known in the art. The other molecules useful in diagnosis, prophylaxis and/or treatment can be administered in a similar dosage regimen as proposed for the binding molecules of the invention. If the other molecules are administered separately, they may be administered to a patient prior to (*e.g.*, 2 min, 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, 2 hrs, 4 hrs, 6 hrs, 8 hrs, 10 hrs, 12 hrs, 14 hrs, 16 hrs, 18 hrs, 20 hrs, 22 hrs, 24 hrs, 2 days, 3 days, 4 days, 5 days, 7 days, 2 weeks, 4 weeks or 6 weeks before), concomitantly with, or subsequent to (*e.g.*, 2 min, 5 min, 10 min, 15 min, 30 min, 45 min, 60 min, 2 hrs, 4 hrs, 6 hrs, 8 hrs, 10 hrs, 12 hrs, 14 hrs, 16 hrs, 18 hrs, 20 hrs, 22 hrs, 24 hrs, 2 days, 3 days, 4 days, 5 days, 7 days, 2 weeks, 4 weeks or 6 weeks after) the administration of one or more of the human binding molecules or pharmaceutical compositions of the invention. The exact dosing regimen is usually sorted out during clinical trials in human patients.

Human binding molecules and pharmaceutical compositions comprising the human binding molecules are particularly useful, and often preferred, when to be administered to human beings as *in vivo* therapeutic agents, since recipient immune response to the administered antibody will often be substantially less than that occasioned by administration of a monoclonal murine, chimeric or humanized binding molecule.

In another aspect, the invention concerns the use of the binding molecules such as neutralizing human monoclonal antibodies (functional fragments and variants thereof), immunoconjugates, nucleic acid molecules, compositions or pharmaceutical compositions according to the invention in the preparation of a medicament for the diagnosis, prophylaxis, treatment, or combination thereof, of an influenza virus H5N1 infection.

Next to that, kits comprising at least a binding molecule such as a neutralizing human monoclonal antibody (functional fragments and variants thereof), at least an immunoconjugate, at least a nucleic acid molecule, at least a composition, at least a pharmaceutical composition, at least a vector, at least a host according to the invention or a combination thereof are also a part of the present invention. Optionally, the above-described components of the kits of the invention are packed in suitable containers and labelled for diagnosis, prophylaxis and/or treatment of the indicated conditions. The above-mentioned components may be stored in unit or multi-dose containers as an aqueous, preferably sterile, solution or as a lyophilised, preferably sterile, formulation for reconstitution. The containers may be formed from a variety of materials such as glass or plastic and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The kit may further comprise more containers comprising a pharmaceutically acceptable buffer. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, culture medium for one or more of the suitable hosts and, possibly, even at least one other therapeutic, prophylactic or diagnostic agent. Associated with the kits can be instructions customarily included in commercial packages of therapeutic, prophylactic or diagnostic products, that contain information about for example the indications, usage, dosage, manufacture, administration, contra-indications and/or warnings concerning the use of such therapeutic, prophylactic or diagnostic products.

The invention further pertains to a method of detecting influenza virus H5N1 in a sample, wherein the method comprises the steps of (a) contacting a sample with a diagnostically effective amount of a binding molecule (functional fragments and variants thereof) or an immunoconjugate according to the invention, and (b) determining whether the binding molecule or immunoconjugate specifically binds to a molecule of the sample. The sample may be a biological sample including, but not limited to blood, serum, stool, sputum, nasophargyal aspirates, bronchial lavages, urine, tissue or other biological material from (potentially) infected subjects, or a non-biological sample such as water, drink, etc. The (potentially) infected subjects may be human subjects, but also animals that are suspected as carriers of influenza virus H5N1 might be tested for the presence of the virus using the human binding molecules or immunoconjugates of the invention. The sample may first be

manipulated to make it more suitable for the method of detection. Manipulation means *inter alia* treating the sample suspected to contain and/or containing the virus in such a way that the virus will disintegrate into antigenic components such as proteins, (poly)peptides or other antigenic fragments. Preferably, the human binding molecules or immunoconjugates of the invention are contacted with the sample under conditions which allow the formation of an immunological complex between the human binding molecules and the virus or antigenic components thereof that may be present in the sample. The formation of an immunological complex, if any, indicating the presence of the virus in the sample, is then detected and measured by suitable means. Such methods include, *inter alia*, homogeneous and heterogeneous binding immunoassays, such as radio-immunoassays (RIA), ELISA, immunofluorescence, immunohistochemistry, FACS, BIACORE and Western blot analyses.

Preferred assay techniques, especially for large-scale clinical screening of patient sera and blood and blood-derived products are ELISA and Western blot techniques. ELISA tests are particularly preferred. For use as reagents in these assays, the binding molecules or immunoconjugates of the invention are conveniently bonded to the inside surface of microtiter wells. The binding molecules or immunoconjugates of the invention may be directly bonded to the microtiter well. However, maximum binding of the binding molecules or immunoconjugates of the invention to the wells might be accomplished by pre-treating the wells with polylysine prior to the addition of the binding molecules or immunoconjugates of the invention. Furthermore, the binding molecules or immunoconjugates of the invention may be covalently attached by known means to the wells. Generally, the binding molecules or immunoconjugates are used between 0.01 to 100 μg/ml for coating, although higher as well as lower amounts may also be used. Samples are then added to the wells coated with the binding molecules or immunoconjugates of the invention.

Furthermore, binding molecules of the invention can be used to identify specific binding structures of influenza virus H5N1. The binding structures can be epitopes on proteins and/or polypeptides. They can be linear, but also structural and/or conformational. In one embodiment, the binding structures can be analysed by means of PEPSCAN analysis (see *inter alia* WO 84/03564, WO 93/09872, Slootstra *et al.*, 1996). Alternatively, a random peptide library comprising peptides from a protein of influenza virus H5N1 can be screened for peptides capable of binding to the binding molecules of the invention. The binding

structures/peptides/epitopes found can be used as vaccines and for the diagnosis of influenza virus H5N1 infections. In case fragments other than proteins and/or polypeptides are bound by the binding molecules, binding structures can be identified by mass spectrometry, high performance liquid chromatography and nuclear magnetic resonance.

In a further aspect, the invention provides a method of screening a binding molecule (or a functional fragment or variant thereof) for specific binding to the same epitope of influenza virus H5N1, as the epitope bound by a human binding molecule of the invention, wherein the method comprises the steps of (a) contacting a binding molecule to be screened, a binding molecule of the invention and influenza virus H5N1 or a fragment thereof, (b) measure if the binding molecule to be screened is capable of competing for specifically binding to influenza virus H5N1 or a fragment thereof with the binding molecule of the invention. In a further step it may be determined, if the screened binding molecules that are capable of competing for specifically binding to influenza virus H5N1 or a fragment thereof have neutralizing activity. A binding molecule that is capable of competing for specifically binding to influenza virus H5N1 or a fragment thereof with the binding molecule of the invention is another part of the present invention. In the above-described screening method, "specifically binding to the same epitope" also contemplates specific binding to substantially or essentially the same epitope as the epitope bound by the a binding molecule of the invention. The capacity to block, or compete with, the binding of the binding molecules of the invention to influenza virus H5N1 typically indicates that a binding molecule to be screened binds to an epitope or binding site on influenza virus H5N1 that structurally overlaps with the binding site on influenza virus H5N1 that is immunospecifically recognized by the binding molecules of the invention. Alternatively, this can indicate that a binding molecule to be screened binds to an epitope or binding site which is sufficiently proximal to the binding site immunospecifically recognized by the binding molecules of the invention to sterically or otherwise inhibit binding of the binding molecules of the invention to influenza virus H5N1.

In general, competitive inhibition is measured by means of an assay, wherein an antigen composition, *i.e.* a composition comprising influenza virus H5N1 or fragments thereof, is admixed with reference binding molecules, *i.e.* the binding molecules of the invention, and binding molecules to be screened. Usually, the binding molecules to be screened are present in excess. Protocols based upon ELISAs and Western blotting are

suitable for use in such simple competition studies. By using species or isotype secondary antibodies one will be able to detect only the bound reference binding molecules, the binding of which will be reduced by the presence of a binding molecule to be screened that recognizes substantially the same epitope. In conducting a binding molecule competition study between a reference binding molecule and any binding molecule to be screened (irrespective of species or isotype), one may first label the reference binding molecule with a detectable label, such as, *e.g.*, biotin, an enzymatic, a radioactive or other label to enable subsequent identification. Binding molecules identified by these competition assays ("competitive binding molecules" or "cross-reactive binding molecules") include, but are not limited to, antibodies, antibody fragments and other binding agents that bind to an epitope or binding site bound by the reference binding molecule, *i.e.* a binding molecule of the invention, as well as antibodies, antibody fragments and other binding agents that bind to an epitope or binding site sufficiently proximal to an epitope bound by the reference binding molecule for competitive binding between the binding molecules to be screened and the reference binding molecule to occur. Preferably, competitive binding molecules of the invention will, when present in excess, inhibit specific binding of a reference binding molecule to a selected target species by at least 10%, preferably by at least 25%, more preferably by at least 50%, and most preferably by at least 75%-90% or even greater. The identification of one or more competitive binding molecules that bind to about, substantially, essentially or at the same epitope as the binding molecules of the invention is a straightforward technical matter. As the identification of competitive binding molecules is determined in comparison to a reference binding molecule, *i.e.* a binding molecule of the invention, it will be understood that actually determining the epitope to which the reference binding molecule and the competitive binding molecule bind is not in any way required in order to identify a competitive binding molecule that binds to the same or substantially the same epitope as the reference binding molecule.

EXAMPLES

To illustrate the invention, the following examples are provided. The examples are not intended to limit the scope of the invention in any way.

Example 1

Construction of scFv phage display libraries using RNA extracted from memory B cells

Peripheral blood was collected from normal healthy donors by venapuncture in EDTA anti-coagulation sample tubes. A blood sample (45 ml) was diluted twice with PBS and 30 ml aliquots were underlayed with 10 ml Ficoll-Hypaque (Pharmacia) and centrifuged at 900xg for 20 min at room temperature without breaks. The supernatant was removed carefully to just above the white layer containing the lymphocytic and thrombocytic fraction. Next, this layer was carefully removed (~10 ml), transferred to a fresh 50 ml tube and washed three times with 40 ml PBS and spun at 400xg for 10 min at room temperature to remove thrombocytes. The obtained pellet containing lymphocytes was resuspended in RPMI medium containing 2% FBS and the cell number was determined by cell counting. Approximately $1x10^8$ lymphocytes were stained for fluorescent cell sorting using CD24, CD27 and surface IgM as markers for the isolation of IgM memory B cells. A Becton Dickinson Digital Vantage apparatus set in Yield Mode was used for physical memory B cell sorting and isolation. Lymphocytes were gated as the small compact population from the FSC/SSC window. Memory B cells (CD24+/CD27+) were subsequently separated from naive B cells (CD24+/CD27-) and memory T cells (CD24-/CD27+). In a next step, IgM memory B cells (IgM+) were separated from switch memory B cells (IgM-) using IgM expression. In this step IgM memory B cells were sorted in a separate sample tube. $1x10^5$ cells were collected in DMEM/50% FBS and after completion of the sort they were centrifuged at 400xg for 10 min and lysed in 500 µl TRIZOL total RNA extraction solution (Invitrogen). The RNA was extracted from the lysis solution using 200 µl chloroform and isopropanol precipitation as detailed in the TRIZOL solution protocol. Next, 1 µl Pellet Paint (Novogen) was applied to enhance and visualize the pelleting process. The complete RNA preparation was dissolved in 23 µl DEPC treated ultrapure water (Invitrogen) and used for cDNA conversion with SuperScript III Reverse Transcriptase (Invitrogen). 1 µl Random Hexamers (500 ng/µl) (Promega) was added to the RNA sample and mixed and melted at 65°C for 5 min in a heated

lid PCR machine. The sample was snap-cooled on wet-ice and the following components were added: 8 µl 5X RT buffer (250 mM Tris-HCl pH 8.3, 375 mM KCl, 15 mM $MgCl_2$), 2 µl dNTPs (10 mM of each) (Invitrogen), 2 µl DTT (100 mM), 2 µl RNAse Inhibitor (40 U/µl) (Promega), 2 µl SuperScript III (200 U/µl) (Invitrogen). The obtained mixture was first incubated for 5 min at room temperature and then transferred to a heated lid PCR machine at 50°C for one hr. The reaction was stopped by heating up to 75°C for 15 min. The cDNA obtained was diluted to 200 µl with ultrapure water and stored at -20°C until further use.

A two round PCR amplification approach was applied using the primer sets shown in Tables 1 and 2 to isolate the immunoglobulin VH and VL regions from the respective donor repertoire. The PCR formulation for amplification used throughout the procedure was as follows: 5 µl cDNA template, 32.75 µl ultrapure water, 2.5 µl of each primer (10 µM), 5 µl 10X PCR buffer (200 mM Tris-HCl pH 8.4, 500 mM KCl), 1.5 µl $MgCl_2$ (50 mM), 0.5 µl dNTP's (25 mM of each), 0.25 µl Taq polymerase (5 U/µl) (Invitrogen). First round amplification on the respective cDNA using the primer sets mentioned in Table 1 yielded 7, 6 and 9 products of about 650 base pairs for respectively VH, Vkappa and Vlambda regions. For IgM memory B cell VH region amplification the OCM constant primer was used in combination with OH1 to OH7. The thermal cycling program for first round amplifications was: 2 min 96°C (denaturation step), 30 cycles of 30 sec 96°C/ 30 sec 55°C/ 60 sec 72°C, 10 min 72°C final elongation and 4°C refrigeration. The products were loaded on and isolated from a 1% agarose gel using gel-extraction columns (Qiagen) and eluted in 50 µl 1 mM Tris-HCl pH 8.0. Ten percent of first round products (5 µl) was subjected to second round amplification using the primers mentioned in Table 2. These primers were extended with restriction sites enabling the directional cloning of the respective VL and VH regions into phage display vector PDV-C06. The PCR program for second round amplifications was as follows: 2 min 96°C (denaturation step), 30 cycles of 30 sec 96°C/ 30 sec 60°C/ 60 sec 72°C, 10 min 72°C final elongation and 4°C refrigeration. The second round products (~350 base pairs) were first pooled according to natural occurrence of J segments found in immunoglobulin gene products, resulting in 7, 6 and 9 pools for respectively the VH, Vkappa and Vlambda variable regions (see Tables 3 and 4). To obtain a normalized distribution of immunoglobulin sequences in the immune library the 6 Vkappa and 9 Vlambda light chain pools were mixed according to the percentages mentioned in Table 3. This single final VL

pool (3 μg) was digested overnight with SalI and NotI restriction enzymes, loaded on and isolated from a 1.5% agarose gel (~350 base pairs) using Qiagen gel-extraction columns and ligated in SalI-NotI cut PDV-C06 vector (~5000 base pairs) as follows: 10 μl PDV-C06 vector (50 ng/μl), 7 μl VL insert (10 ng/μl), 5 μl 10X ligation buffer (NEB), 2.5 T4 DNA Ligase (400 U/μl) (NEB), 25.5 μl ultrapure water (vector to insert ratio was 1:2). Ligation was performed overnight in a water bath of 16°C. Next, the volume was doubled with water, extracted with an equal volume of phenol-chloroform-isoamylalcohol (75:24:1) (Invitrogen) followed by chloroform (Merck) extraction and precipitated with 1 μl Pellet Paint (Novogen), 10 μl sodium acetate (3 M pH 5.0) and 100 μl isopropanol for 2 hrs at -20°C. The obtained sample was subsequently centrifuged at 20.000xg for 30 min at 4°C. The obtained precipitate was washed with 70% ethanol and centrifuged for 10 min at 20.000xg at room temperature. Ethanol was removed by vacuum aspiration and the pellet was air dried for several min and then dissolved in 50 μl buffer containing 10 mM Tris-HCl, pH 8.0. 1 μl ligation mixture was used for the transformation of 40 μl TG-1 electro-competent cells (Stratagene) in a chilled 0.1 cm electroporation cuvette (Biorad) using a Genepulser II apparatus (Biorad) set at 1.7 kV, 200 Ohm, 25 μF (time constant ~4,5 msec). Directly after pulse, the bacteria were flushed from the cuvette with 1000 μl SOC medium (Invitrogen) containing 5% (w/v) glucose (Sigma) at 37°C and transferred to a 15 ml round bottom culture tube. Another 500 μl SOC/glucose was used to flush residual bacteria from the cuvette and was added to the culture tube. Bacteria were recovered by culturing for exactly one hr at 37°C in a shaker incubator at 220 rpm. The transformed bacteria were plated over large 240 mm square petridishes (NUNC) containing 200 ml 2TY agar (16 g/l bacto-tryptone, 10 g/l bacto-yeast extract, 5 g/l NaCl, 15 g/l agar, pH 7.0) supplemented with 50 μg/ml ampicillin and 5% (w/v) glucose (Sigma). A 1 to 1000 dilution was plated for counting purposes on 15 cm petridishes containing the same medium. This transformation procedure was repeated sequentially twenty times and the complete library was plated over a total of thirty large square petridishes and grown overnight in a 37°C culture stove. Typically, around $1x10^7$ cfu were obtained using the above protocol. The intermediate VL light chain library was harvested from the plates by mildly scraping the bacteria into 10 ml 2TY medium per plate. The cell mass was determined by OD600 measurement and two times 500 OD of bacteria was used for maxi plasmid DNA

preparation using two P500 maxiprep columns (Qiagen) according to manufacturer's instructions.

Analogous to the VL variable regions, the second round VH-JH products were first mixed together to obtain the normal J segment usage distribution (see Table 4), resulting in 7 VH subpools called PH1 to PH7. The pools were mixed to acquire a normalized sequence distribution using the percentages depicted in Table 4, obtaining one VH fraction that was digested with SfiI and XhoI restriction enzymes and ligated in SfiI-XhoI cut PDV-VL intermediate library obtained as described above. The ligation set-up, purification method, subsequent transformation of TG1 and harvest of bacteria was exactly as described for the VL intermediate library (see above). The final library (approximately $5x10^6$ cfu) was checked for insert frequency with a colony PCR using a primer set flanking the inserted VH-VL regions. More than 95% of the colonies showed a correct length insert (see Table 5). The colony PCR products were used for subsequent DNA sequence analysis to check sequence variation and to assess the percentage of colonies showing a complete ORF. This was typically above 70% (see Table 5). The frequency of mutations in the V genes was also analysed. Out of 50 sequences, 47 (94%) were not in germline configuration indicative of a maturation process and consistent with the memory phenotype of the B cells used as an RNA source for the library. Finally, the library was rescued and amplified by using CT helper phages (see WO 02/103012) and was used for phage antibody selection by panning methods as described below.

Example 2

Selection of phages carrying single chain Fv fragments against H5N1

Antibody fragments were selected using antibody phage display libraries constructed essentially as described above and general phage display technology and MABSTRACT® technology essentially as described in US Patent Number 6,265,150 and in WO 98/15833 (both of which are incorporated by reference herein). Furthermore, the methods and helper phages as described in WO 02/103012 (which is incorporated by reference herein) were used in the present invention.

Selection was performed against recombinant hemagglutinin (HA) subtype H5 (A/Vietnam/1203/2004; see SEQ ID NO:110) produced using baculovirus vectors in insect

cells (Protein Sciences, CT, USA). The amino acid sequence of HA from isolate A/Vietnam/1194/2004 (H5N1TV) and the consensus amino acid sequence representing HAs from strains isolated in Indonesia and China (H5N1IC) are shown in SEQ ID NO:111 and SEQ ID NO:112, respectively. Selections were also performed against soluble recombinant HA (sHA) from H5N1. The sequence encoding for the extracellular (soluble) part of HA (sHA) from isolate A/Vietnam/1194/2004 (H5N1), representing the HAs identified in influenza strains isolated in Thailand and Vietnam (sHA of H5N1TV, SEQ ID NO:113) in 2004 (clade 1) and a consensus sequence representing soluble parts of HAs of H5N1 strains isolated in Indonesia and China (sHA of H5N1IC, SEQ ID NO:114) in 2003/2004 (clade 2) were cloned in an expression vector containing a myc- and his-tag using standard DNA cloning techniques. HAs of H5N1TV and H5N1IC differ at 9 amino acid positions, all located in the HA1 subunit of the molecules. DNA transfections were performed in PER.C6 cells for transient and/or stable expression using standard techniques. sHA was purified from culture supernatant using metal chelate affinity chromatography using HisTrap™ FF Columns (Amersham Biosciences) according to the manufacturer's instructions.

HA antigens (recombinant HA and sHA of H5N1TV) were diluted in PBS (5.0 μg/ml), added to MaxiSorp™ Nunc-Immuno Tubes (Nunc) and incubated overnight at 4°C on a rotating wheel. The immunotubes were emptied and washed three times in block buffer (2% non-fat dry milk (ELK) in PBS). Subsequently, the immunotubes were filled completely with block buffer and incubated for 1-2 hrs at room temperature. In addition, immunotubes were coated overnight with anti-myc antibody and incubated with block buffer containing 5 μg/ml myc-tagged sHA of H5N1TV. Aliquots of pooled phage display library (500-1000 μl, $0.5x10^{13}$ – $1x10^{13}$ cfu, amplified using CT helper phage (see WO 02/103012)) were blocked in blocking buffer supplemented with 10% non-heat inactivated fetal bovine serum and 2% mouse serum for 1-2 hrs at room temperature. The blocked phage library was added to the immunotubes, incubated for 2 hrs at room temperature, and washed with wash buffer (0.05% (v/v) Tween-20 in PBS) to remove unbound phages. Bound phages were eluted from the respective antigen by incubation with 1 ml of 100 mM triethylamine (TEA) for 10 min at room temperature. Subsequently, the eluted phages were mixed with 0.5 ml of 1 M Tris-HCl pH 7.5 to neutralize the pH. This mixture was used to infect 5 ml of an XL1-Blue *E.coli* culture that had been grown at 37°C to an OD 600 nm of approximately 0.3. The phages were

allowed to infect the XL1-Blue bacteria for 30 min at 37°C. Then, the mixture was centrifuged for 10 min at 3000xg at room temperature and the bacterial pellet was resuspended in 0.5 ml 2-trypton yeast extract (2TY) medium. The obtained bacterial suspension was divided over two 2TY agar plates supplemented with tetracycline, ampicillin and glucose. After incubation overnight of the plates at 37°C, the colonies were scraped from the plates and used to prepare an enriched phage library, essentially as described by De Kruif *et al.* (1995a) and WO 02/103012. Briefly, scraped bacteria were used to inoculate 2TY medium containing ampicillin, tetracycline and glucose and grown at a temperature of 37°C to an OD 600 nm of ~0.3. CT helper phages were added and allowed to infect the bacteria after which the medium was changed to 2TY containing ampicillin, tetracycline and kanamycin. Incubation was continued overnight at 30°C. The next day, the bacteria were removed from the 2TY medium by centrifugation after which the phages in the medium were precipitated using polyethylene glycol (PEG) 6000/NaCl. Finally, the phages were dissolved in 2 ml of PBS with 1% bovine serum albumin (BSA), filter-sterilized and used for the next round of selection.

Alternatively, phage selections using full-length HA-expressing cell lines were performed. To this end, expression vectors containing the complete coding sequence of full-length HA from isolate A/Vietnam/1194/2004 (H5N1TV) and a consensus sequence representing full-length HAs of H5N1 strains isolated in Indonesia and China (H5N1IC) were used to transfect PER.C6 cells. Flow cytometry analysis using an anti-HA antibody was performed in parallel with each phage selection to assure HA expression by H5N1TV- and H5N1IC-transfected PER.C6 cells (data not shown). $10x10^6$ untransfected PER.C6 cells were resuspended in 0.5 ml pooled phage library and 0.5 ml PER.C6 culture medium supplemented with 4% ELK and incubated for 1 hr in an end-over-end rotor set at 5 rpm at 4°C. After 5 min centrifugation at 300xg at 4°C of the phage library/untransfected PER.C6 cell mixture, the supernatant containing the phages was subtracted for a second time with $10x10^6$ untransfected PER.C6 cells. The subtracted phage preparation was subsequently mixed with $1x10^6$ HA-expressing PER.C6 cells and incubated for 2 hrs in an end-over-end rotor set at 5 rpm at 4°C. Subsequently, the cells were spun for 2 min at 3000xg and the cell pellet was resuspended in 1 ml PBS/0.05% Tween-20 to wash away unbound phages. The cells were centrifuged for 2 min at 3000xg and the washing was repeated for an additional 5 times. After each wash the

cells were transferred to a new tube. Bound phages were eluted from the antigen by incubation with 1 ml of 100 mM TEA for 10 min in an end-over-end rotor set at 5 rpm at room temperature. The cells were spun for 2 min at 3000xg and the eluted phages were transferred to a 50 ml tube containing 0.5 ml 1 M Tris-HCl, pH 7.5. Rescue and propagation of the eluted phages was performed as described above. Two rounds of selections were performed before isolation of individual single-chain phage antibodies. After the second round of selection, individual *E.coli* colonies were used to prepare monoclonal phage antibodies. Essentially, individual colonies were grown to log-phase in 96 well plate format and infected with VCS-M13 helper phages after which phage antibody production was allowed to proceed overnight. The supernatants containing phage antibodies were used directly in ELISA for binding to HA antigens. Alternatively, phage antibodies were PEG/NaCl-precipitated and filter-sterilized for flow cytometry analysis.

Example 3

Validation of the HA specific single-chain phage antibodies

Selected single-chain phage antibodies that were obtained in the screening described above were validated in ELISA for specificity, *i.e.* binding to HA antigens. For this purpose, baculovirus expressed recombinant HA (Protein Sciences, CT, USA) and purified sHAs of H5N1TV and H5N1IC were coated to Maxisorp™ ELISA plates. Anti-myc mA 9E10 (Roche) was immobilized on Maxisorp™ ELISA plates as negative control antigen. After coating, the plates were washed three times with PBS containing 0.1% v/v Tween-20 and blocked in PBS containing 3% BSA or 2% ELK for 1 hr at room temperature. The selected single-chain phage antibodies were incubated for 1 hr in an equal volume of PBS containing 4% ELK to obtain blocked phage antibodies. The plates were emptied, washed three times with PBS/0.1% Tween-20 and the blocked single-chain phage antibodies were added to the wells. Incubation was allowed to proceed for one hr, the plates were washed with PBS/0.1% Tween-20 and bound phage antibodies were detected (using OD 492nm measurement) using an anti-M13 antibody conjugated to peroxidase. As a control, the procedure was performed simultaneously without single-chain phage antibody and with a negative control single-chain phage antibody. From the selections on the different HA antigens with the IgM memory B

cell library, 92 unique single-chain phage antibodies specific for either recombinant HA or sHA were obtained.

Alternatively, the reactivity of single chain antibodies that were selected for binding to HA-expressing PER.C6 cells was tested using flow cytometry analysis. PEG/NaCl precipitated phages were mixed with an equal volume of PBS/2% ELK blocked for 30 min on ice. The blocked phages were added to pelleted cells (untransfected PER.C6 and HA-expressing PER.C6 cells) and incubated for one hr on ice. The cells were washed three times with PBS/1% BSA, followed by a 1 minute centrifugation at 300xg, and binding of the single chain phage antibodies to the cells was visualized using a biotinylated anti-M13 antibody (Fitzgerald) followed by streptavidin-phycoerythrin conjugate (Caltag). The selections using HA-expressing PER.C6 cells provided 24 unique single-chain phage antibodies that were not identified during selections using the different recombinant HA proteins.

Example 4

Characterization of the HA specific scFvs

From the selected specific single-chain phage antibodies (scFv) clones plasmid DNA was obtained and nucleotide and amino acid sequences were determined according to standard techniques. The nucleotide and amino acid sequence and VH and VL gene identity (see Tomlinson IM et al. V-BASE Sequence Directory. Cambridge United Kingdom: MRC Centre for Protein Engineering (1997)) of the scFvs are depicted in Table 6. The CDR regions of the HA- specific immunoglobulins are shown in Table 7.

Example 5

Construction of fully human immunoglobulin molecules (human monoclonal antibodies) from the selected single chain Fvs

Heavy and light chain variable regions of the scFvs were cloned directly by restriction digest for expression in the IgG expression vectors pIg-C911-HCgamma1 (see SEQ ID No:141), pIG-C909-Ckappa (see SEQ ID NO:142), or pIg-C910-Clambda (see SEQ ID No:143). Nucleotide sequences for all constructs were verified according to standard techniques known to the skilled artisan. The resulting expression constructs encoding the human IgG1 heavy and light chains were transiently expressed in combination in 293T cells and supernatants

containing human IgG1 antibodies were obtained and produced using standard purification procedures. The human IgG1 antibodies were titrated in a concentration range of between 10 and 0.003 μg/ml against H5 (data not shown). A SARS-CoV specific antibody was included as a control antibody. The IgG1 molecules showed the same pattern of reactivity as demonstrated for the single-chain phage antibodies.

The nucleotide and amino acid sequences of the heavy and light chain of the antibodies called CR6141, CR6255, CR6257, CR6260, CR6261, CR6262, CR6268, CR6272, CR6296, CR6301, CR6307, CR6310, CR6314, CR6323, CR6325, CR6327, CR6328, CR6329, CR6331, CR6332, CR6334, CR6336, CR6339, CR6342, CR6343 and CR6344 as well as their heavy and light chain variable regions are given in Table 8. Subsequently, binding of the anti-HA IgG to HA-expressing PER.C6 cells was investigated by flow cytometry. Flow cytometry analysis for antibody binding to HA demonstrated that antibodies CR6255, CR6257, CR6260, CR6261, CR6262, CR6268, CR6307, CR6310, CR6314, CR6323, CR6325, CR6331 and CR6344 bound to HA (H5N1TV)-expressing PER.C6 cells (see Table 9). Antibodies CR6261 and CR6344 also displayed binding to untransfected control cells, but the obtained signals were approximately 10-fold lower than the signals obtained for binding to HA (H5N1TV)-expressing PER.C6 cells (see Table 9). No binding of control antibody CR3014 to HA-expressing cells and untransfected control cells was observed.

Example 6

In vitro neutralization of H5N1 influenza virus by H5N1 specific IgGs (virus neutralization assay)

In order to determine whether the selected IgGs were capable of blocking H5N1 infection, *in vitro* virus neutralization assays (VNA) were performed. The VNA were performed on MDCK cells (ATCC CCL-34). MDCK cells were cultured in MDCK cell culture medium (MEM medium supplemented with antibiotics, 20 mM Hepes and 0.15% (w/v) sodium bicarbonate (complete MEM medium), supplemented with 10% (v/v) fetal bovine serum). The H5N1 reassortant strain NIBRG-14 which was used in the assay was diluted to a titer of $4x10^3$ TCID50/ml (50% tissue culture infective dose per ml), with the titer calculated according to the method of Spearman and Karber. The IgG preparations (200 μg/ml) were

serially 2-fold diluted (1:2 - 1:16) in complete MEM medium in duplicate wells. 25 µl of the respective IgG dilution was mixed with 25 µl of virus suspension (100 TCID50/25 µl) and incubated for one hr at 37°C. The suspension was then transferred in duplicate onto 96-well plates containing confluent MDCK cultures in 50 µl complete MEM medium. Prior to use, MDCK cells were seeded at $3x10^4$ cells per well in MDCK cell culture medium, grown until cells had reached confluence, washed with 300-350 µl PBS, pH 7.4 and finally 50 µl complete MEM medium was added to each well. The inoculated cells were cultured for 3-4 days at 33°C and observed daily for the development of cytopathic effect (CPE). CPE was compared to the positive control (NIBRG-14-inoculated cells) and negative controls (mock-inoculated cells). The complete absence of CPE in an individual cell culture was defined as protection. Sheep anti-A/Vietnam/1194/04 H5N1 influenza virus HA (04/214, NIBSC) was used as a positive control in the assay.

In addition, cultures were tested for the presence of virus using immunohistochemistry. To this end, the culture supernatant was discarded and the cells were fixed with 40% (v/v) acetone and 60% (v/v) methanol for 15 min. Fixed cells were blocked for 30 min at 37°C in blocking buffer (200 mM NaCl, 0.2% (w/v) bovine serum albumin (BSA), 0.01% thimerosal, 0.2% (v/v) Tween-20, 20 mM Tris-HCl, pH 7.45) supplemented with 2% (w/v) BSA and 5% (v/v) goat serum. Subsequently, cells were incubated for one hr at 37°C with 50 µl mouse anti-influenza A monoclonal antibody blend (Chemicon) diluted 1:1000 in washing buffer. After three washes with washing buffer, 50 µl of biotin-conjugated goat anti-mouse IgG (Jackson) diluted 1:1000 in washing buffer was added and incubated for one hr at 37°C. After three washes with washing buffer, 50 µl of streptavidin-peroxidase conjugate (Calbiochem) diluted 1:3000 in washing buffer was added and incubated for 30 min at 37°C. After another three washes with washing buffer, staining was visualized using AEC solution (0.12% (w/v) 3-amino-9-ethylcarbazole, 30% (v/v) N-N-dimethylformamide and 70% (v/v) acetate buffer) containing 1 µl H_2O_2/1 ml AEC solution. After three washes with washing buffer, staining was analysed under a microscope.

The human anti-HA antibodies called CR6255, CR6257, CR6260, CR6261, CR6262, CR6268, CR6307, CR6310, CR6314, CR6323, CR6325, CR6331 and CR6344 were subjected to the above-described VNA. All antibodies neutralized H5N1 reassortant strain NIBRG-14. The concentrations (in µg/ml) at which these antibodies protect MDCK cultures

against CPE are given in Table 10. In wells where CPE was observed, the presence of virus was confirmed by immunohistochemical staining (data not shown).

In order to determine the neutralizing potency of the H5N1 specific IgGs more accurately, the *in vitro* virus neutralization assays with NIBRG-14 was repeated, but this time the IgG preparations were further diluted. The IgG preparations (200 μg/ml) were serially 2-fold diluted (1:1 - 1:512) in complete MEM medium and tested in quadruplicate wells in the VNA as described above. The neutralizing potency of the human anti-H5N1 antibodies called CR6255, CR6257, CR6260, CR6261, CR6262, CR6268, CR6272, CR6307, CR6310, CR6314, CR6323, CR6325, CR6327, CR6328, CR6329, CR6331, CR6332, CR6334, CR6336, CR6339, CR6342, CR6343 and CR6344 was determined in the VNA. All antibodies, except CR6272 and CR6339, neutralized H5N1 reassortant strain NIBRG-14. The concentrations (in μg/ml, in the presence of 100 TCID50 of virus) at which these antibodies protect MDCK cultures against CPE are indicated in Table 11. In wells where CPE was observed, the presence of virus was confirmed by immunohistochemical staining (data not shown).

Example 7

Immunoblot analysis of H5N1 specific IgGs

To further investigate the specificity of the anti-HA antibodies, different recombinant hemagglutinin Influenza A antigens were subjected to SDS-PAGE under reducing conditions followed by anti-HA immunoblot analysis. The HA0 polypeptide is composed of the HA1 and HA2 subunit. Antibody CR5111, a H5N1-specific control antibody, recognized the HA1 subunit and the intact (uncleaved) HA0 polypeptide of sHA of H5N1TV (see Fig 1, right part, lane 1). In addition, CR5111 recognized the HA1 subunit of recombinant HA, subtype H5 (A/Vietnam/1203/2004 (H5N1); see SEQ ID NO:110) produced using baculovirus vectors in insect cells (Protein Sciences, CT, USA) (Fig 1, right part, lane 2). Uncleaved HA0 polypeptide was not detected in this HA preparation. The difference in size between the HA subunits in lanes 1 and 2 might be explained by a different glycosylation of HA expressed in insect cells and PER.C6 cells. CR5111 did not recognize the HA1 and/or HA0 polypeptides of recombinant HA, subtype H1 (A/New Caledonia/20/99 (H1N1)) (see Fig 1, right part, lane 4) or of recombinant HA, subtype H3 (A/Wyoming/3/2003(H3N2)) (Fig 1, right part, lane 3).

Antibodies CR6307 and CR6323 recognized the HA2 subunits of sHA of H5N1TV (see Fig 1, left and middle part, lanes 1) and recombinant HA, subtype H5 (A/Vietnam/1203/2004 (H5N1) (see Fig 1, left and middle part, lanes 2). Interestingly, the HA2 subunit as present in the intact, uncleaved HA0 polypeptides was not recognized. Apparently, the epitope recognized by CR6307 and CR6323 becomes accessible upon cleavage of HA0. In addition, antibodies CR6307 and CR6323 recognized the HA2 subunit of recombinant HA, subtype H1 (A/New Caledonia/20/99 (H1N1)) (see Fig 1, left and middle part, lanes 4), but not the HA2 subunit of recombinant HA, subtype H3 (A/Wyoming/3/2003(H3N2)) (see Fig 1, left and middle part, lanes 3), both recombinant HAs produced using baculovirus vectors in insect cells (Protein Sciences, CT, USA). Because the binding site of neutralizing antibodies CR6307 and CR6323 is conserved within influenza A strains of the subtype H1 and H5, a molecule comprising the binding site could be considered as (part of a) vaccine capable of inducing a broadly cross-reactive anti-influenza antibody response.

Next to antibodies CR6307 and CR6323, the antibodies called CR6141, CR6296, and CR6301 were used in immunoblot analysis. Each of the three antibodies was able to bind to the HA2 subunit of sHA of H5N1TV and recombinant HA, subtype H5 (A/Vietnam/1203/2004; H5N1) (data not shown).

Example 8

FACS analysis to determine the subunit specificity of H5N1 specific IgGs

In order to evaluate the contribution of the HA1 subunit to binding of anti-H5N1 antibodies, an assay was set up, wherein the HA1 subunit is released from HA-expressing PER.C6 cells. HA-expressing PER.C6 cells were washed three times with PBS, pH 7.4, and incubated for 10 min in acidified PBS, pH 4.9. Subsequently, the cells were washed with PBS, pH 7.4, and treated for 10 min with 10 μg/ml trypsin in PBS, pH 7.4, to cleave HA0 molecules into disulfide bond-linked HA1 and HA2 subunits. Finally, the cells were incubated for 20 min in 20 mM DTT in PBS, pH 7.4, to release the HA1 subunit from the membrane-anchored HA2 subunit. Untreated and acid/trypsin/DTT-treated cells were washed twice with PBS containing 1% w/v BSA. For flow cytometry analysis, $2.5x10^5$ cells were used per staining. No staining of treated and untreated cells with the negative control antibody CR3014 was observed.

Antibody CR5111, which binds to the HA1 subunit in immunoblot analysis, stained the population of untreated HA-expressing PER.C6 cells, while treated cells were not recognized (data not shown). This provides further proof that CR5111 recognizes the HA1 subunit. Treated and untreated cells were stained to a similar extent by the antibodies CR6307 and CR6323 (data not shown). Release of the HA1 subunit obviously did not influence binding of these antibodies further substantiating the results from the immunoblot analysis that the antibodies bind to the HA2 subunit. Antibodies CR6325 and CR6331 bound to untreated cells, while binding to treated cells was markedly reduced compared with binding to untreated cells (data not shown). This suggests that the affinity of the antibodies for their epitope is significantly reduced by the conformational change induced upon acid treatment or by the reduction of the disulfide bond that links the HA1 and HA2 subunit.

Example 9

Hemagglutinin competition ELISA with phage antibodies and IgGs

To identify antibodies that bind to non-overlapping, non-competing epitopes, a hemagglutinin competition ELISA was performed. Nunc-Immuno™ Maxisorp F96 plates were coated overnight at 4°C with 0.5 µg/ml recombinant HA, subtype H5 (A/Vietnam/1203/2004 (H5N1) (Protein Sciences) in PBS. Uncoated protein was washed away before the wells were blocked with 300 µl PBS containing 2% w/v non-fat dry milk (blocking solution) for 1 hr at room temperature. The blocking solution was discarded and 50 µl of 10 µg/ml anti-H5N1 IgG in blocking solution was incubated per well for 1 hr at room temperature. Subsequently, 50 µl of phage antibody in blocking solution in a concentration twice of the concentration that resulted in 50% maximal binding (as determined in a previous assay) was added per well and incubated for another hr at room temperature. Wells were washed three times with PBS containing 0.1% v/v Tween-20. Bound phage antibody was detected using a peroxidase-conjugated anti-M13 antibody. Wells were washed again as described above and the ELISA was further developed by the addition of 100 µl of OPD reagent (Sigma). The reaction was stopped by adding 50 µl 1 M H_2SO_4 and then the OD at 492 nm was measured. Binding of phage antibody, in the presence of IgG, was expressed as percentage of binding in the absence of IgG, which was set at 100%. Phage antibody SC05-111 and corresponding IgG CR5111,

which recognize an epitope in the HA1 subunit of H5 hemagglutinin were included as controls.

The results indicate that the majority of the phage antibodies and IgGs bind to an overlapping epitope on recombinant HA, subtype H5 (A/Vietnam/1203/2004 (H5N1)) (data not shown). Binding of SC05-111 phage antibody was blocked by CR5111 IgG, but not by any other IgG, suggesting that the other IgGs recognize an epitope different from the binding region of CR5111. Five IgGs, CR6262, CR6272, CR6307, CR6339 and CR6343 competed to a lower extent for binding than the rest of the IgGs (more than 25% residual binding). For IgGs CR6262, CR6272, CR6339, and CR6343 this can be explained by a lower affinity for HA. This is supported by the observation that the phage antibodies corresponding to these antibodies were competed away more efficiently by the other IgGs. Binding of phage antibody SC06-307 is blocked by IgG CR6307, but less efficiently by the other IgGs. This suggests that SC06-307 and CR6307 recognize a unique epitope which differs from the epitope recognized by the other IgGs.

Example 10

Cross-reactivity ELISA using anti-H5N1 IgGs

To test whether the epitope of the anti-H5N1 antibodies is conserved among HAs other than subtype H5, a hemagglutinin cross-reactivity ELISA was performed. Nunc-Immuno™ Maxisorp F96 plates (Nunc) were coated overnight at 4°C with 0.5 μg/ml recombinant HA, subtype H1 (A/New Caledonia/20/99 (H1N1)), subtype H3 (A/Wyoming/3/03 (H3N2)), subtype H5 (A/Vietnam/1203/04 (H5N1)), subtype H7 (A/Netherlands/219/03 (H7N7)), and subtype H9 (A/Hong Kong/1073/99 (H9N2)) (Protein Sciences Corp.) in PBS. Additionally, BPL-inactivated virus preparations containing 0.5 μg/ml of HA of A/New Caledonia/20/99 (H1N1), and reassortant strain NIBRG-14 (A/Vietnam/1194/04 (H5N1)) were coated on the plates overnight in PBS. Wells were washed three times with PBS containing 0.1% v/v Tween-20 to remove uncoated protein and subsequently blocked with 300 μl PBS containing 2% w/v non-fat dry milk (blocking solution) for 1 hr at room temperature. The blocking solution was discarded and 100 μl per well of 5 μg/ml anti-H5N1 antibodies in blocking solution was incubated for 1 hr at room temperature. Wells were washed three times with PBS containing 0.1% v/v Tween-20 and bound antibodies were detected using a peroxidase-

conjugated mouse anti-human IgG antibody (Jackson). The reaction was developed and measured as described *supra*. Table 12 shows that all anti-H5N1 IgGs bound to recombinant HA, subtype H5 (A/Vietnam/1203/2004 (H5N1)) and a BPL-inactivated virus preparation of NIBRG-14, which contains the HA of strain A/Vietnam/1194/2004 (H5N1). Recombinant HAs of subtype H3 and H7 were not recognized by any of the tested anti-H5N1 IgGs. Interestingly, all anti-H5N1 IgGs, with the exception of CR5111 and CR6307, bound to recombinant HA of subtypes H1 and H9, and a BPL-inactivated virus preparation of strain A/New Caledonia/20/99 (H1N1). This indicates that the epitope of the majority of the anti-H5N1 IgGs is conserved among HA molecules of different subtypes.

Example 11

Epitope mapping of anti-H5N1 IgGs

Okuno et al. (1993) and Smirnov et al. (1999) demonstrated the existence of a common epitope shared by the HAs of the influenza A virus subtypes H1, H2, and H5 and neutralization of these subtypes by the murine monoclonal antibody C179 directed against this epitope. This conformational epitope is composed of two different sites which are located in the HA1 and HA2 subunit. Both sites are located in close proximity in the middle of the stem region of the HA molecule. In order to evaluate whether the anti-HA antibodies described *supra* recognized this epitope, HA molecules containing amino acid substitutions in this region were made.

The epitope recognized by antibody C179 (Takara Bio Inc.) has been attributed to regions encompassing residues 318-322 of the HA1 subunit and residues 47-58 of the HA2 subunit (amino acid numbering as described by Okuno et al.1999). Escape viruses containing HAs that carry a Thr to Lys substitution at position 318 in the HA1 subunit or a Val to Glu substitution at position 52 in the HA2 subunit were no longer recognized and neutralized by C179. These mutations (position 318 Thr to Lys, mutant I; position 52 Val to Glu, mutant II), a Leu to Met substitution at position 320 in the HA1 subunit (mutant III, Met320 is present in region 318-322 of HA1 of subtype H3 and H7), a Ser to Arg substitution at position 54 in the HA2 subunit (mutant IV, Arg54 is present in region 47-58 of HA2 of subtype H3 and H7) and an Asp to Asn substitution at position 57 in the HA2 subunit (mutant V, Asn57 is present in region 47-58 of HA2 of strain A/Hong Kong/156/97 (H5N1)) were introduced in full-length

HA from isolate A/Vietnam/1194/2004 (H5N1TV) and tranfected in PER.C6 cells. Binding of C179 and the human anti-HA antibodies to PER.C6 cells expressing these mutants was evaluated by FACS analysis as described *supra*. Antibody CR5111, which is directed against an epitope in the HA1 subunit, and a polyclonal anti-H5 sheep serum confirmed the expression of H5N1TV and HA mutants by transfected PER.C6 cells (data not shown). No staining with the negative control antibody CR3014 or in the absence of antibody was observed (data not shown). As expected, antibody C179 did not recognize mutants I and II, which carried the same amino acid substitutions as the HAs in the C179 escape viruses (see Okuno *et al.*, 1993). Furthermore, C179 did not bind to mutant IV, whereas binding of C179 to mutants III and V was unaffected. A similar pattern of reactivity was observed for antibody CR6342, which suggests that antibody C179 and CR6342 recognize a similar epitope. Antibodies CR6261, CR6325 and CR6329 recognized all mutants, with the exception of mutant II. This suggests that the epitope of antibodies CR6261, CR6325 and CR6329 is different from that of C179. Since substitutions in the HA1 subunit did not abrogate binding of these antibodies, their epitope is most likely located in the HA2 subunit. Antibodies CR6307 and CR6323 recognized all mutants, which suggests that also the epitope of these antibodies is different from that of C179. A summary of the sequence of the mutants and binding of the antibodies is given in Table 13. In conclusion, the results indicate that antibodies CR6261, CR6325, CR6329, CR6307 and CR6323 are ideal candidates to bind to and neutralize influenza viruses that have mutations in the epitope recognized by the murine monoclonal antibody C179 and as a consequence thereof are no longer neutralized by this antibody.

Example 12

Prophylactic activity of human IgG monoclonal antibodies against lethal H5N1 challenge in vivo

A lethal dose of influenza H5N1 strain A/HongKong/156/97 was administered to mice in order to study the prophylactic effect of human monoclonal IgG antibodies CR6261, CR6323 and CR6325. One day prior to infection 8 groups of 10 mice each were injected intraperitoneally with different doses of antibody. As a negative control one group of mice was injected with a non-relevant control antibody (CR3014). Clinical signs, weight loss and

mortality were monitored until 21 days after infection. This study was conducted to assess the prophylactic effect of the monoclonal human anti-H5N1 IgG antibodies in vivo.

The H5N1 strain was originally obtained from a 3-year-old child suffering from respiratory disease. The virus was passaged two times on MDCK cells. The batch [Titre 8.1 log $TCID_{50}$ /ml] used to infect mice was propagated once in embryonated eggs.

80 female 7-week-old Balb/c mice were divided in the 8 groups of 10 mice each with the following injections prior to challenge with the H5N1 virus:

1. 15 mg/kg CR6261.
2. 5 mg/kg CR6261.
3. 2 mg/kg CR6261.
4. 0.7 mg/kg CR6261.
5. 15 mg/kg CR6323.
6. 15 mg/kg CR6325
7. 500µl rabbit anti-H5N3 immune serum (100x diluted).
8. 15 mg/kg CR3014.

All animals were acclimatized and maintained for a period of 6 days prior to the start of the study. One day prior to infection with H5N1 virus, 500 µl of antibody was administered by intraperitoneal injection. The animals were inoculated intranasally on day 0 with 25 LD_{50} of virus (approximately 50 µl), and followed for 21 days. The actual dose of the virus administered was estimated by titrating a few replicate samples from the inoculum remaining after inoculation of the animals was completed. Virus titers (TCID50/mL) of the inoculum were determined on MDCK cells. The results showed that no inactivation of virus had unintentionally occurred during preparation or administration of the inoculum. Group 8 acted as negative control. The animals in this group were injected with an irrelevant monoclonal antibody (CR3014) on day 0. Group 7 was supposed to act as positive control. The mice in this group were injected with a rabbit polyclonal serum antibody raised against H5N3 influenza virus.

Clinical signs and weights were assessed daily from day –1 until 21 days after virus inoculation. Clinical signs were scored with a scoring system (0 = no clinical signs; 1 = rough coat; 2 = rough coat, less reactive, passive during handling; 3 = rough coat, rolled up,

laboured breathing, passive during handling; 4 = rough coat, rolled up, laboured breathing, does not roll back on stomach when laid down on its back) and recorded. Surviving animals were euthanised and bled on day 21. For analysis of serum IgG antibody levels blood samples were collected from each mouse on day 0. Sera were prepared according to standard procedure. To generate post infection sera, blood was collected from surviving animals on day 21. Sera were stored at -20 °C ± 2°C until assayed for the presence of virus specific antibodies. Sera were tested in duplicate using 4 HAU of the H5N1 HK/97 substrate. Titers were expressed as the reciprocal of the highest serum dilution showing HI, starting at a dilution of 1/10.

All mice were active and appeared healthy without showing signs of disease during the acclimatization period. The average clinical score (total clinical score divided by number of surviving animals in each group) was calculated per day and the results are indicated in Fig 2 (average clinical score per group), Table 14 (clinical scores) and Table 15 (respiratory distress). Onset of negative clinical signs was observed at day 3 after infection in the group that was inoculated with the negative control Ab CR3014 (group 8). Respiratory distress was first recorded on day 6, and lasted for 1 to 4 days. No clinical signs were observed in mice that were treated with 15 mg/kg of CR6325 (group 6). In group 5 (CR6323), one mouse showed mild clinical signs (score 1) from day 5 to 8 and died the next day. In group 1, one mice died on day 13 without having shown any previous clinical signs. Higher Ab doses of CR6261 correlated with later onset and lower clinical scores on average. Respiratory distress was noticed in the lowest dose group (0.7 mg/kg), but not in the higher dose groups (2, 5 and 15 mg/kg). All mice showed improvement in their clinical condition between day 9 and 13 (group 2, 3 and 5) or from day 17 on (group 4). Mice that were injected with the rabbit polyclonal antibody (group 7) developed severe illness within 3 days and then died, demonstrating that the rabbit antibody did not protect against infection in vivo. Two animals (one in group 4 and one in group 8) were euthanized on day 10 and removed from the study, because the animals were considered to be severely ill (score 4).

The animals infected with H5N1 showed varying degrees of weight loss (Fig 3). Proportional weight loss and the moment of onset were related to antibody dose. In the groups treated with the highest dose of antibodies weight steadily increased over time consistent with age-related weight gain. The group of animals inoculated with the lowest dose of CR6261 lost

weight more quickly than the groups of animals receiving higher doses of antibody. The total amount of weight loss was greater in the lower dose groups, with average weight loss of about 15 and 40% of starting weight in the groups inoculated with 2 and 0.7 mg/kg CR6261, respectively. In the lower dose groups average body weight appeared to increase again at the same time as animals showed some clinical improvement.

Fig 4 shows the number of mice surviving per group on each day. A clear dose-response relationship between the amount of antibody administered and average survival time was present. Fig 5 shows the mortality in a dose-responsive manner. The first mice died 7 days after inoculation in the lowest dose group (0.7 mg/kg) and in the group of mice that received the negative control: CR3014. Less than 50% of the animals were protected against death when 0.7 mg/kg of CR6261 antibody was administered. However, 9 to 10 mice survived when the highest dose of antibody was administered. No mice of the negative control group (CR3014) survived, showing that indeed a 100% lethal challenge dose was used in this study.

To assess whether IgG antibodies are able to render complete protection against infection, an HI assay is performed with sera collected at day 21 from mice that had received 15 mg/kg of CR6261 (group 1). This data should indicate that the mice experienced an H5N1 infection albeit without clinical manifestation.

These results show that at least three human anti-H5N1 antibodies, identified and developed as disclosed herein (CR6261, CR6323 and CR6325) are each separately able to provide protection against a lethal dose of influenza H5N1 <u>in vivo</u>. A clear dose-response relationship between the amount of CR6261 antibody administered and average survival time was observed. The results show that each monoclonal anti-H5N1 IgG antibody tested was able to prevent clinical manifestation of H5N1 infection in mice when administered one day prior to infection at a dose of 15 mg/kg.

<u>Example 13</u>

Protective and therapeutic effects of human monoclonal anti-H5N1 antibodies administered after an infection with a lethal dose of influenza H5N1 virus <u>in vivo</u>

A study was performed to test the therapeutic effect of the monoclonal antibodies as disclosed herein, exemplified by CR6261, in a post-infection model, against a lethal H5N1 A/HK/97

influenza virus challenge in vivo. The virus batch and the type, and age of mice were the same as used in example 12. As a negative control one group of mice was injected with a non-relevant control antibody (CR2006). Clinical signs, weight loss and mortality were monitored until 21 days after infection.

58 female 7-week-old Balb/c mice were divided in 5 groups that received the antibody at different stages after infection, as follows:

1. 10 mice; 15 mg/kg CR6261 at 4 hr post infection
2. 14 mice; 15 mg/kg CR6261 at 1 day post infection
3. 10 mice; 15 mg/kg CR6261 at 2 days post infection
4. 10 mice; 15 mg/kg CR6261 at 3 days post infection
5. 14 mice; 15 mg/kg CR2006 at 1 day post infection

All animals were acclimatized and maintained for a period of 6 days prior to the start of the study. The animals were inoculated intranasally on day 0 with 25 LD_{50} of H5N1 influenza virus (approximately 50 µl), and monitored for 21 days. The actual dose of the virus administered was estimated by titrating a few replicate samples from the inoculum remaining after inoculation of the animals was completed. Virus titers (TCID50/mL) of the inoculum were determined on MDCK cells. The results showed that no inactivation of virus had unintentionally occurred during preparation or administration of the inoculum. At the specified time points after inoculation, 500 µl of antibody was administered by intraperitoneal injection. Group 5 acted as negative control. The animals in this group were injected with an irrelevant monoclonal antibody (CR2006) day 1 post-infection.

Clinical signs and weights were assessed each day from day –1 until day 21. Clinical signs were scored as described in example 12, with a scoring range from 0 to 4. Surviving animals were euthanised and bled on day 21. For assessment of pathological changes, 4 animals of group 2 and 5 were killed on day 6 after challenge. These animals were already pre-selected on day 0, and set apart from the others. For that reason, groups 2 and 5 started with 14 animals, with 10 mice remaining after the selection. Clinical signs and weights were assessed daily from day –1 until 21 days after virus inoculation.

All mice were active and appeared healthy without showing signs of disease during the acclimatization period. The average clinical score (total clinical score divided by number of surviving animals in each group) was calculated per day and the results are indicated in Fig 6 (average clinical score per group), Table 16 (clinical scores) and Table 17 (respiratory distress). Clearly, all groups contained mice that showed clinical signs already at day 1 after infection. Depending on the time at which the antibody was administered, the clinical signs diminished and in all groups clinical signs were absent again at day 15. In the control group 5, all animals suffered from severe clinical signs and all animals had died, or were euthanized because they reached level 4 in the clinical scores, at day 9. This shows that again a lethal dose of influenza virus was administered to the animals. In Group 1, wherein the animals already received the antibody 4 hr after infection, some animals did not develop clinical signs, whereas others did. The number of animals that did exhibit clinical signs that could be scored are provided in Table 16. Since influenza virus can have a dramatic effect on the respiratory organs, also the respiratory distress was measured and here provided in Table 17. Fig 7 and Table 18 show the number of surviving animals and the mortality rate respectively for all groups. For unknown reasons, one animal in group 1 that received the antibody 4 hr after infection died at day 10. All remaining animals in the groups that received the antibody after the influenza infection survived and were healthy at day 21. This is clearly shown in the body weight data that was obtained from all mice. Fig 8 shows the mean body weight in each group of mice during the 21 days of the study. Although the body weight of all mice decreased upon infection, the body weight did return to normal levels after administration of the antibody. Clearly, the return to normal body weight levels depended on the timing of the antibody treatment, where animals that were treated 4 hr after exposure, recovered rapidly and reached normal levels at day 7, the animals that were treated 3 days after infection, reached their normal body weight at day 17. All animals reached a similar and healthy body weight at the end of the study, at day 21. Clearly, all animals that received the negative control antibody did not regain body weight and measurements stopped at death at day 9.

These results show that a post-infection treatment with a monoclonal antibody directed against H5N1 influenza virus, as disclosed herein and exemplified by antibody CR6261, can rescue mammalian subjects, as showed herein in mice, after challenge with a lethal dose of H5N1 influenza virus. Even at a late stage, 3 days post-infection, the antibody is

able to reverse the clinical symptoms to a level in which no clinical signs could be monitored anymore. Strikingly, at day 21 post-infection, all antibody-treated animals reached normal body weight levels and did not show any remaining clinical signs.

Example 14

In vivo cross-protection against lethal challenge by heterologous influenza subtypes using monoclonal antibodies directed against HA of H5N1.

As disclosed supra (example 11), some of the antibodies of the present invention apparently recognize a single epitope in the HA2 domain of the H5 haemagglutinin protein. In example 7 it was shown that certain binding molecules of the present invention could interact with the HA2 epitope in a non-conformational manner, in other words, the form in which the haemagglutinin protein is folded does not seem to hinder the neutralizing activity and the protective effects of these antibodies as disclosed herein.

The sequences of the influenza haemagglutinin protein parts that are not prone to antigenic drift (= the change of immunodominant regions within the HA1 region of the protein, resulting in the need for yearly updated influenza vaccines) are known in the art. The epitope in HA2 that is recognized by CR6261, CR6325 and CR6329 is contained in the amino acid sequence GVTNKVNSIIDK (SEQ ID NO:368, see Table 13) and is also present in the haemagglutinin proteins of H1 and H9 subtypes, see Table 22. It was shown in example 10 that interaction of the binding molecules of the present invention to the epitope was not limited to HA from H5, but that also HA from H1 and H9 were recognized (see Table 12). Hence, the binding molecules of the present invention recognize an epitope that is present in multiple HA proteins from different influenza serotypes.

To study the cross-applicability of these antibodies for therapy in vivo, an experiment was performed in mice that was in line with the dosing schedule of the experiment described in example 13. In the present experiment, a very high, lethal dose of another influenza virus related to the 1918 pandemic outbreak and now circulating seasonally in humans, namely H1N1, was administered in mice. Subsequently, the mice were treated with an antibody of the present invention, exemplified by CR6261, and clinical signs, respiratory distress and body weight were monitored for 3 weeks after infection. It turned out that these binding molecules

that could rescue mice when infected with H5N1, were also able to rescue mammalian subjects when infected with H1N1, as outlined below.

A study was performed to test the therapeutic effect of the monoclonal antibodies, exemplified by CR6261, in a post-infection model against a lethal H1N1 A/WSN/33 influenza virus challenge in vivo. The virus batch was obtained from ATCC (VR-219) and was once propagated in embryonated eggs. The titre was 8.5 log $TCID_{50}$/ml. As a negative control one group of mice was injected with an irrelevant monoclonal antibody (IgG1, λ named 'CR57', isotype matched negative control antibody). Clinical signs, weight loss and mortality were monitored until 21 days after infection.

50 female 6 to 8-week-old Balb/c mice were divided in 5 groups that received the antibody at different stages related to the infection, as follows:

1. 10 mice; 15 mg/kg CR6261 at 1 day prior to infection
2. 10 mice; 15 mg/kg CR6261 at 1 day post infection
3. 10 mice; 15 mg/kg CR6261 at 2 days post infection
4. 10 mice; 15 mg/kg CR6261 at 3 days post infection
5. 10 mice; 15 mg/kg neg. contr. CR57 at 1 day post infection

All animals were acclimatized and maintained for a period of at least 4 days prior to the start of the study. The animals were inoculated intranasally on day 0 with a lethal dose of H1N1 virus (6.6 log $TCID_{50}$; equivalent of 25x the LD_{50}) in approximately 50 µl, and monitored. At the specified time points before/after inoculation, 500 µl of antibody was administered by intraperitoneal injection. General health of the mice was monitored throughout the study. Clinical signs and weights were assessed each day from day –1 until day 21. Clinical signs were scored with the scoring rates as disclosed in example 12 and 13, ranging from 0 to 4. Surviving animals were euthanised and bled on day 21.

The mortality rate for each group is provided in Table 19, showing the number of living mice in each study group throughout the study. Two mice died shortly after the inoculation event (at day 1, one in group 2 and one in group 3) and were excluded from the analysis as pre-defined in the study plan. All mice in the control group 5 were dead at day 9 like in the previous study with H5N1 (see Table 18). The percentage of animals surviving this lethal challenge dose of H1N1 is also plotted in Fig 9. The number of mice showing relevant

clinical signs in each group is provided in Table 20. No clinical signs were observed in Group 1, whereas in Group 2, 3 and 4, some mice displayed clinical signs that disappeared completely after day 14 upon inoculation. All animals in Group 5 started showing clinical signs at day 2. No mice in this group recovered. The number of mice showing respiratory distress in category 2 or 3 is given in Table 21. No clinical distress was observed anymore after day 13 in Groups 1-4, whereas all remaining mice in control Group 5 did suffer from severe respiratory distress.

Fig 10 shows the average body weight of the mice in each study group. Clearly, no measurements are provided for the mice in Group 5 after day 8. As can be seen from this figure, all mice that received the anti-H5N1 antibody and that recovered from the clinical signs did get to their expected body weight level at day 21.

The antibodies could protect these mice when administered before infection or after infection. Notably, the infection dose was rather high: 25x the LD_{50} dose, indicating that the antibodies provide a very strong protection against the virus even when present at high titers in the lung. This is clinically relevant as highly pathogenic viruses like H5N1 replicate to high titer after infection and these high viral loads have been linked to the frequently severe outcome in infected humans. Moreover, all protected mice recovered completely from this lethal infection over time. It is concluded that the anti-H5N1 antibodies of the present invention (such as CR6261, CR6325, and CR6329) that bind to (single) epitopes in the HA2 region, a region that is not prone to antigenic drift, provide cross-protection in vivo against multiple influenza serotypes, circumventing the need for antibodies against the highly mutation-sensitive HA1 region. It is to be understood that the binding molecules of the present invention that are not limited by epitopes that are only present in HA from an H5 influenza serotype, can also be used in the prophylactic-, or therapeutic treatment of all influenza serotypes that contain the same epitope in the stable region of HA2, such as H1N1, and influenza viruses comprising H2, H6 and H9 haemagglutinin proteins.

Example 15

Affinity studies

Affinity studies were performed using surface plasmon resonance analysis with a BIAcore3000 analytical system at 25°C and 37°C, using HBS-EP (Biacore AB, Sweden) as

running buffer at a flow rate of 75 µl/min. IgGs were immobilized on a research grade CM5 4-flow channel (Fc) sensor chip (Biacore AB, Sweden) using amine coupling. A varying amount of HA from an H5N1 virus (A/Vietnam/1203/2004) was injected to analyse the binding interaction between the HA protein and the immobilized IgGs. Regeneration using 20 mM NaOH was performed at the end of each measurement to remove bound HA, while leaving the immobilized IgG on the chip.

Affinity constants were determined for CR6261, CR6323 and CR6325 antibodies. Five concentrations in 4-fold dilutions of HA were injected (100 µl per injection), followed by a dissociation phase of 3600 sec, and regeneration using 10 µl 20 mM NaOH. The resulting data were fitted using a 1:1 (Langmuir) model. However, an accurate dissociation constant (KD) could not be calculated. This was due to extremely low dissociation rates at 25°C (even with an extended measurement) leading to unacceptable error in the calculation. When the experiments were repeated at 37°C discernible dissociation did occur but still not sufficiently enough to accurately measure the KD. Experiments are performed to establish a definitive KD for the antibodies. These are estimated to be at least in the single digit nM range and most likely in the pM range of affinity. These experiments show that the binding molecules of the present invention have a very high affinity for their epitope present in the HA protein of influenza virus.

Below, the details of the nucleic acid and amino acid sequences referred to herein as SEQ ID NO:58-143, SEQ ID NO:212-237, and SEQ ID NO:316-367 are provided.

SEQ ID NO:58

```
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SEQ ID NO:59

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R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K
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SEQ ID NO:60

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SEQ ID NO:61

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T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V
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I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
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SEQ ID NO:62

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SEQ ID NO:63

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A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D
I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
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SEQ ID NO:64

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SEQ ID NO:65

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SEQ ID NO:66

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SEQ ID NO:67

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SEQ ID NO:68

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SEQ ID NO:69

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A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S
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SEQ ID NO:70

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gtagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaggtggt 300
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gaggagatga ccaagaacca ggtgtccctc acctgtctgg tgaagggctt ctaccccagc 1140
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cctgtgctgg acagcgacgg cagcttcttc ctgtacagca agctcaccgt ggacaagagc 1260
cggtggcagc agggcaacgt gttcagctgc agcgtgatgc acgaggccct gcacaaccac 1320
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SEQ ID NO:71

Q V Q L V Q S G G G L V K P G G S L R L S C A A S G F T F S S Y S M N W V R
Q A P G K G L E W V S S I S S S S S Y I Y Y V D S V K G R F T I S R D N A K
N S L Y L Q M N S L R A E D T A V Y Y C A R G G G S Y G A Y E G F D Y W G Q
G T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K
D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V
V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T
H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C
V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T
Y R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S
K A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S
D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D
K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:72

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gcaccgaagt tccagggcag agtcacgatt accgcggacg atttcgcggg cacagtttac 240
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gtgctggaca gcgacggcag cttcttcctg tacagcaagc tcaccgtgga caagagccgg 1260
tggcagcagg gcaacgtgtt cagctgcagc gtgatgcacg aggccctgca caaccactac 1320
acccagaaga gcctgagcct gagccccggc aag 1353

SEQ ID NO:73

E V Q L V E S G A E V K K P G S S V K V S C K A S G G P F R S Y A I S W V R
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G T V Y M E L S S L R S E D T A M Y Y C A K H M G Y Q V R E T M D V W G K G
T T V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D
Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V
T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H
T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V
V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y
R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K
A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D
I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:74

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cctggacaag ggcctgagtg gatgggaggg atcatcccta tttttggtac aacaaaatac     180
gcaccgaagt tccagggcag agtcacgatt accgcggacg atttcgcggg cacagtttac     240
atggagctga gcagcctgcg atctgaggac acggccatgt actactgtgc gaaacatatg     300
gggtaccagg tgcgcgaaac tatggacgtc tggggcaaag ggaccacggt caccgtctcg     360
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agcggcctgt acagcctgag cagcgtggtg accgtgccca gcagcagcct gggcacccag     600
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aacagcacct accgggtggt gagcgtgctc accgtgctgc accaggactg gctgaacggc     960
aaggagtaca agtgcaaggt gagcaacaag gccctgcctg cccccatcga gaagaccatc    1020
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gagatgacca agaaccaggt gtccctcacc tgtctggtga agggcttcta ccccagcgac    1140
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gtgctggaca gcgacggcag cttcttcctg tacagcaagc tcaccgtgga caagagccgg    1260
tggcagcagg gcaacgtgtt cagctgcagc gtgatgcacg aggccctgca caaccactac    1320
acccagaaga gcctgagcct gagccccggc aag                                 1353
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SEQ ID NO:75

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Q A P G Q G P E W M G G I I P I F G T T K Y A P K F Q G R V T I T A D D F A
G T V Y M E L S S L R S E D T A M Y Y C A K H M G Y Q V R E T M D V W G K G
T T V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D
Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V
T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H
T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V
V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y
R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K
A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D
I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:76

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gcacagaact tccagggcag actcacgatt accgcggacg aatccacgag cacagcctac   240
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aagagctgcg acaagaccca cacctgcccc ccctgccctg cccccgagct gctgggcgga   720
ccctccgtgt tcctgttccc ccccaagccc aaggacaccc tcatgatcag ccggacccca   780
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ctggacagcg acggcagctt cttcctgtac agcaagctca ccgtggacaa gagccggtgg  1260
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SEQ ID NO:77

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Q A P G Q G L E W M G D I I G M F G S T N Y A Q N F Q G R L T I T A D E S T
S T A Y M E L S S L R S E D T A V Y Y C A R S S G Y Y P A Y L P H W G Q G T
L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y
F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T
V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T
C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V
V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R
V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A
K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I
A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S
R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K
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SEQ ID NO:78

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cctggacaag gacttgagtg gatgggaggg atcatcccta tgtttggtac aacaaactac   180
gcacagaagt tccagggcag agtcacgatt accgcggtcg aatccacgag cacagcctac   240
atggaggtga gcagcctgag atctgaggac acggccgttt attactgtgc gagaggtgat   300
aagggtatct actactacta catggacgtc tggggcaaag ggaccacggt caccgtctcg   360
agtgctagca ccaagggccc cagcgtgttc cccctggccc ccagcagcaa gagcaccagc   420
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gagatgacca agaaccaggt gtccctcacc tgtctggtga agggcttcta ccccagcgac   1140
atcgccgtgg agtgggagag caacggccag cccgagaaca actacaagac caccccccct   1200
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acccagaaga gcctgagcct gagccccggc aag 1353

SEQ ID NO:79

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S T A Y M E V S S L R S E D T A V Y Y C A R G D K G I Y Y Y Y M D V W G K G
T T V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D
Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V
T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H
T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V
V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y
R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K
A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D
I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:80

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atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagaggaaat 300
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cagaagagcc tgagcctgag ccccggcaag 1350

SEQ ID NO:81

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Q A P G Q G L E W M G G I I G M F G T A N Y A Q K F Q G R V T I T A D E F T
S T A Y M E L S S L R S E D T A V Y Y C A R G N Y Y Y E S S L D Y W G Q G T
L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y
F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T
V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T
C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V
V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R
V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A
K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I
A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S
R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:82

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gcacagaagt tccagggcag agtcacgatt accgcggacg aatcgacgag cactgtctac 240
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accagcggcg gcacagccgc cctgggctgc ctggtgaagg actacttccc cgagcccgtg 480
accgtgagct ggaacagcgg cgccttgacc agcggcgtgc acaccttccc cgccgtgctg 540
cagagcagcg gcctgtacag cctgagcagc gtggtgaccg tgcccagcag cagcctgggc 600
acccagacct acatctgcaa cgtgaaccac aagcccagca acaccaaggt ggacaaacgc 660
gtggagccca agagctgcga caagacccac acctgccccc cctgccctgc ccccgagctg 720
ctgggcggac cctccgtgtt cctgttcccc cccaagccca aggacaccct catgatcagc 780
cggacccccg aggtgacctg cgtggtggtg gacgtgagcc acgaggaccc cgaggtgaag 840
ttcaactggt acgtggacgg cgtggaggtg cacaacgcca agaccaagcc ccgggaggag 900
cagtacaaca gcacctaccg ggtggtgagc gtgctcaccg tgctgcacca ggactggctg 960
aacggcaagg agtacaagtg caaggtgagc aacaaggccc tgcctgcccc catcgagaag 1020
accatcagca aggccaaggg ccagccccgg gagccccagg tgtacaccct gccccccagc 1080
cgggaggaga tgaccaagaa ccaggtgtcc ctcacctgtc tggtgaaggg cttctacccc 1140
agcgacatcg ccgtggagtg ggagagcaac ggccagcccg agaacaacta caagaccacc 1200
cccctgtgc tggacagcga cggcagcttc ttcctgtaca gcaagctcac cgtggacaag 1260
agccggtggc agcagggcaa cgtgttcagc tgcagcgtga tgcacgaggc cctgcacaac 1320
cactacaccc agaagagcct gagcctgagc cccggcaag 1359

SEQ ID NO:83

Q V Q L V Q S G A E V K K P G S S V R V S C K A S G S I F R N Y A M S W V R
Q A P G Q G L E W M G G I I A I F G T P K Y A Q K F Q G R V T I T A D E S T
S T V Y M E L S G L R S E D T A M Y Y C A R I P H Y N F G S G S Y F D Y W G
Q G T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V
K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S
V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K
T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T
C V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S
T Y R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I
S K A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P
S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V
D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:84

tcctatgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60
tcttgttctg gaagcacgtt caacatcgga agtaatgctg tagactggta ccggcagctc 120
ccaggaacgg cccccaaact cctcatctat agtaataatc agcggccctc aggggtccct 180
gaccgattct ctggctccag gtctggcacc tcagcctccc tggccatcag tgggctccag 240
tctgaggatg aggctgatta ttactgtgca gcatgggatg acatcctgaa tgttccggta 300
ttcggcggag ggaccaagct gaccgtccta ggtgcggccg caggccagcc caaggccgct 360
cccagcgtga ccctgttccc cccctcctcc gaggagctgc aggccaacaa ggccacccctg 420
gtgtgcctca tcagcgactt ctaccctggc gccgtgaccg tggcctggaa ggccgacagc 480
agccccgtga aggccggcgt ggagaccacc acccccagca agcagagcaa caacaagtac 540
gccgccagca gctacctgag cctcaccccc gagcagtgga agagccaccg gagctacagc 600
tgccaggtga cccacgaggg cagcaccgtg gagaagaccg tggcccccac cgagtgcagc 660

SEQ ID NO:85

S Y V L T Q P P S A S G T P G Q R V T I S C S G S T F N I G S N A V D W Y R
Q L P G T A P K L L I Y S N N Q R P S G V P D R F S G S R S G T S A S L A I
S G L Q S E D E A D Y Y C A A W D D I L N V P V F G G G T K L T V L G A A A
G Q P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V

T V A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P
E Q W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:86

cagtctgccc tgactcagcc tgccgccgtg tctgggtctc ctggacagtc gatcaccatc 60
tcctgcactg gaaccagcag tgacgttggt ggttataact atgtctcctg gtaccaacag 120
cacccaggca aagcccccaa actcatgatt tatgaggtca gtaatcggcc ctcaggggtt 180
tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240
caggctgagg acgaggctga ttattactgc agctcatata caagcagcag cacttatgtc 300
ttcggaactg ggaccaaggt caccgtccta ggtgcggccg caggccagcc caaggccgct 360
cccagcgtga ccctgttccc cccctcctcc gaggagctgc aggccaacaa ggccaccctg 420
gtgtgcctca tcagcgactt ctaccctggc gccgtgaccg tggcctggaa ggccgacagc 480
agccccgtga aggccggcgt ggagaccacc acccccagca agcagagcaa caacaagtac 540
gccgccagca gctacctgag cctcaccccc gagcagtgga agagccaccg gagctacagc 600
tgccaggtga cccacgaggg cagcaccgtg gagaagaccg tggcccccac cgagtgcagc 660

SEQ ID NO:87

Q S A L T Q P A A V S G S P G Q S I T I S C T G T S S D V G G Y N Y V S W Y
Q Q H P G K A P K L M I Y E V S N R P S G V S N R F S G S K S G N T A S L T
I S G L Q A E D E A D Y Y C S S Y T S S S T Y V F G T G T K V T V L G A A A
G Q P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V
T V A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P
E Q W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:88

tcctatgtgc tgactcagcc accctcagtc tctgggaccc ccgggcagag ggtcaccatc 60
tcttgctctg gaagccgctc caacgtcgga gataattctg tatattggta tcaacacgtc 120
ccagaaatgg cccccaaact cctcgtctat aagaatactc aacggccctc aggagtccct 180
gcccggtttt ccggctccaa gtctggcact tcagcctccc tggccatcat tggcctccag 240
tccggcgatg aggctgatta ttattgtgtg gcatgggatg acagcgtaga tggctatgtc 300
ttcggatctg ggaccaaggt caccgtccta ggtgcggccg caggccagcc caaggccgct 360
cccagcgtga ccctgttccc cccctcctcc gaggagctgc aggccaacaa ggccaccctg 420
gtgtgcctca tcagcgactt ctaccctggc gccgtgaccg tggcctggaa ggccgacagc 480
agccccgtga aggccggcgt ggagaccacc acccccagca agcagagcaa caacaagtac 540
gccgccagca gctacctgag cctcaccccc gagcagtgga agagccaccg gagctacagc 600
tgccaggtga cccacgaggg cagcaccgtg gagaagaccg tggcccccac cgagtgcagc 660

SEQ ID NO:89

S Y V L T Q P P S V S G T P G Q R V T I S C S G S R S N V G D N S V Y W Y Q
H V P E M A P K L L V Y K N T Q R P S G V P A R F S G S K S G T S A S L A I
I G L Q S G D E A D Y Y C V A W D D S V D G Y V F G S G T K V T V L G A A A
G Q P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V
T V A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P
E Q W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:90

cagtctgtgt tgacgcagcc gccctcagtg tctgcggccc caggacagaa ggtcaccatc 60
tcctgctctg gaagcagctc caacattggg aatgattatg tatcctggta ccagcagctc 120
ccaggaacag cccccaaact cctcatttat gacaataata agcgaccctc agggattcct 180
gaccgattct ctggctccaa gtctggcacg tcagccaccc tgggcatcac cggactccag 240
actggggacg aggccaacta ttactgcgca acatgggatc gccgcccgac tgcttatgtt 300
gtcttcggcg gagggaccaa gctgaccgtc ctaggtgcgg ccgcaggcca gcccaaggcc 360
gctcccagcg tgaccctgtt ccccccctcc tccgaggagc tgcaggccaa caaggccacc 420
ctggtgtgcc tcatcagcga cttctaccct ggcgccgtga ccgtggcctg gaaggccgac 480
agcagccccg tgaaggccgg cgtggagacc accacccca gcaagcagag caacaacaag 540
tacgccgcca gcagctacct gagcctcacc cccgagcagt ggaagagcca ccggagctac 600
agctgccagg tgacccacga gggcagcacc gtggagaaga ccgtggcccc caccgagtgc 660

agc 663

SEQ ID NO:91

Q S V L T Q P P S V S A A P G Q K V T I S C S G S S S N I G N D Y V S W Y Q
Q L P G T A P K L L I Y D N N K R P S G I P D R F S G S K S G T S A T L G I
T G L Q T G D E A N Y Y C A T W D R R P T A Y V V F G G G T K L T V L G A A
A G Q P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A
V T V A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T
P E Q W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:92

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcgagtca gggcattagc agttatttag cctggtatca gcagaagcca 120
gggaaagttc ctacactcct gatctatgat gcatccactt tgcgatcagg ggtcccatct 180
cgcttcagtg gcagtggatc tgcgacagat ttcactctca ccatcagcag cctgcagcct 240
gaagatgttg caacttatta ctgtcaaagg tataacagtg ccccccccgat caccttcggc 300
caagggacac gactggagat taaacgtgcg gccgcaccca gcgtgttcat cttcccccc 360
tccgacgagc agctgaagag cggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420
ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480
gagagcgtga ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctcacc 540
ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaggtgac ccaccagggc 600
ctgagcagcc ccgtgaccaa gagcttcaac cggggcgagt gt 642

SEQ ID NO:93

D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q G I S S Y L A W Y Q Q
K P G K V P T L L I Y D A S T L R S G V P S R F S G S G S G S A T D F T L T I S
S L Q P E D V A T Y Y C Q R Y N S A P P I T F G Q G T R L E I K R A A A P S
V F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W K V D N
A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K
V Y A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:94

cagtctgtgc tgactcagcc accctcagag tccgtgtccc caggacagac agccagcgtc 60
acctgctctg gacataaatt gggggataaa tatgtttcgt ggtatcagca gaagccaggc 120
cagtcccctg tattactcat ctatcaagat aacaggcggc cctcagggat ccctgagcga 180
ttcataggct ccaactctgg gaacacagcc actctgacca tcagcgggac ccaggctctg 240
gatgaggctg actattactg tcaggcgtgg gacagcagca ctgcggtttt cggcggaggg 300
accaagctga ccgtcctagg tgcggccgca ggccagccca aggccgctcc cagcgtgacc 360
ctgttccccc cctcctccga ggagctgcag gccaacaagg ccaccctggt gtgcctcatc 420
agcgacttct accctggcgc cgtgaccgtg gcctggaagg ccgacagcag ccccgtgaag 480
gccggcgtgg agaccaccac ccccagcaag cagagcaaca acaagtacgc cgccagcagc 540
tacctgagcc tcacccccga gcagtggaag agccaccgga gctacagctg ccaggtgacc 600
cacgagggca gcaccgtgga gaagaccgtg gcccccaccg agtgcagc 648

SEQ ID NO:95

Q S V L T Q P P S E S V S P G Q T A S V T C S G H K L G D K Y V S W Y Q Q K
P G Q S P V L L I Y Q D N R R P S G I P E R F I G S N S G N T A T L T I S G
T Q A L D E A D Y Y C Q A W D S S T A V F G G G T K L T V L G A A A G Q P K
A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V T V A W
K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P E Q W K
S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:96

gaaattgtgc tgactcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gcgtgttagc agctacttag cctggtacca acagaaacct 120
ggccaggctc ccaggctcct catctatggt gcatccacca gggccgctgg catcccagac 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag actggagcct 240
gaagattctg cagtgtatta ctgtcagcag tatggtagga caccgctcac tttcggcgga 300
gggaccaagg tggagatcaa acgtgcggcc gcacccagcg tgttcatctt ccccccctcc 360
gacgagcagc tgaagagcgg caccgccagc gtggtgtgcc tgctgaacaa cttctacccc 420
cgggaggcca aggtgcagtg gaaggtggac aacgccctgc agagcggcaa cagccaggag 480
agcgtgaccg agcaggacag caaggactcc acctacagcc tgagcagcac cctcaccctg 540
agcaaggccg actacgagaa gcacaaggtg tacgcctgcg aggtgaccca ccagggcctg 600
agcagccccg tgaccaagag cttcaaccgg ggcgagtgt 639

SEQ ID NO:97

E I V L T Q S P G T L S L S P G E R A T L S C R A S Q R V S S Y L A W Y Q Q
K P G Q A P R L L I Y G A S T R A A G I P D R F S G S G S G T D F T L T I S
R L E P E D S A V Y Y C Q Q Y G R T P L T F G G G T K V E I K R A A A P S V
F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W K V D N A
L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K V
Y A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:98

tcctatgtgc tgactcagcc accctcggtg tcagtggccc caggacagac ggccaggatt 60
acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120
caggcccctg tgctggtcgt ctatgatgat agcgaccggc cctcagggat ccctgagcga 180
ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240
gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatgc tgtgttcgga 300
ggaggcaccc agctgaccgt cctcggtgcg gccgcaggcc agcccaaggc cgctcccagc 360
gtgaccctgt tccccccctc ctccgaggag ctgcaggcca acaaggccac cctggtgtgc 420
ctcatcagcg acttctaccc tggcgccgtg accgtggcct ggaaggccga cagcagcccc 480
gtgaaggccg gcgtggagac caccacccca agcaagcaga gcaacaacaa gtacgccgcc 540
agcagctacc tgagcctcac ccccgagcag tggaagagcc accggagcta cagctgccag 600
gtgacccacg agggcagcac cgtggagaag accgtggccc ccaccgagtg cagc 654

SEQ ID NO:99

S Y V L T Q P P S V S V A P G Q T A R I T C G G N N I G S K S V H W Y Q Q K
P G Q A P V L V V Y D D S D R P S G I P E R F S G S N S G N T A T L T I S R
V E A G D E A D Y Y C Q V W D S S S D H A V F G G G T Q L T V L G A A A G Q
P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V T V
A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P E Q
W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:100

tcctatgtgc tgactcagcc accctcagcg tctgggaccc ccgggcagag ggtcaccatc 60
tcttgttctg gaagcagctc caacatcgga agtaattatg tatactggta ccagcagctc 120
ccaggcacgg cccccaaact cctcatctat agggatggtc agcggccctc aggggtccct 180
gaccgattct ctggctccaa gtctggcacc tcagcctccc tggccatcag tggactccgg 240
tccgatgatg aggctgatta ttactgtgca acatgggatg acaacctgag tggtccagta 300
ttcggcggag ggaccaagct gaccgtccta ggtgcggccg caggccagcc caaggccgct 360
cccagcgtga ccctgttccc cccctcctcc gaggagctgc aggccaacaa ggccaccctg 420
gtgtgcctca tcagcgactt ctaccctggc gccgtgaccg tggcctggaa ggccgacagc 480
agccccgtga aggccggcgt ggagaccacc acccccagca agcagagcaa caacaagtac 540
gccgccagca gctacctgag cctcacccccc gagcagtgga agagccaccg gagctacagc 600
tgccaggtga cccacgaggg cagcaccgtg gagaagaccg tggcccccac cgagtgcagc 660

SEQ ID NO:101

S Y V L T Q P P S A S G T P G Q R V T I S C S G S S S N I G S N Y V Y W Y Q
Q L P G T A P K L L I Y R D G Q R P S G V P D R F S G S K S G T S A S L A I
S G L R S D D E A D Y Y C A T W D D N L S G P V F G G G T K L T V L G A A A
G Q P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V

T V A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P
E Q W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:102

gaaattgtgt tgacccagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcacccag aactttcggc 300
ggagggacca aggtggagat caaacgtgcg gccgcaccca gcgtgttcat cttcccccc 360
tccgacgagc agctgaagag cggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420
ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480
gagagcgtga ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctcacc 540
ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaggtgac ccaccagggc 600
ctgagcagcc ccgtgaccaa gagcttcaac cggggcgagt gt 642

SEQ ID NO:103

E I V L T Q S P G T L S L S P G E R A T L S C R A S Q S V S S S Y L A W Y Q
Q K P G Q A P R L L I Y G A S S R A T G I P D R F S G S G S G T D F T L T I
S R L E P E D F A V Y Y C Q Q Y G S S P R T F G G G T K V E I K R A A A P S
V F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W K V D N
A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K
V Y A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:104

cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 60
tcctgcactg gaaccagcag tgacgttggt ggttataact atgtctcctg gtaccaacag 120
cacccaggca aagcccccaa actcatgatt tatgaggtca gtaatcggcc ctcaggggtt 180
tctaatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 240
caggctgagg acgaggctga ttattactgc agctcatata caagcagcag cactcttgtc 300
ttcggaactg ggaccaaggt caccgtccta ggtgcggccg caggccagcc caaggccgct 360
cccagcgtga ccctgttccc cccctcctcc gaggagctgc aggccaacaa ggccaccctg 420
gtgtgcctca tcagcgactt ctaccctggc gccgtgaccg tggcctggaa ggccgacagc 480
agccccgtga aggccggcgt ggagaccacc acccccagca agcagagcaa caacaagtac 540
gccgccagca gctacctgag cctcacccc gagcagtgga agagccaccg gagctacagc 600
tgccaggtga cccacgaggg cagcaccgtg gagaagaccg tggcccccac cgagtgcagc 660

SEQ ID NO:105

Q S A L T Q P A S V S G S P G Q S I T I S C T G T S S D V G G Y N Y V S W Y
Q Q H P G K A P K L M I Y E V S N R P S G V S N R F S G S K S G N T A S L T
I S G L Q A E D E A D Y Y C S S Y T S S S T L V F G T G T K V T V L G A A A
G Q P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V
T V A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P
E Q W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:106

cagtctgtcg tgacgcagcc gccctcggtg tcagtggccc caggacagac ggccaggatt 60
acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120
caggcccctg tgctggtcgt ctatgatgat agcgaccggc cctcagggat ccctgagcga 180
ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240
gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatta tgtcttcgga 300
actgggacca aggtcaccgt cctaggtgcg gccgcaggcc agcccaaggc cgctcccagc 360
gtgaccctgt tccccccctc ctccgaggag ctgcaggcca acaaggccac cctggtgtgc 420
ctcatcagcg acttctaccc tggcgccgtg accgtggcct ggaaggccga cagcagcccc 480
gtgaaggccg gcgtggagac caccaccccc agcaagcaga gcaacaacaa gtacgccgcc 540
agcagctacc tgagcctcac ccccgagcag tggaagagcc accggagcta cagctgccag 600
gtgacccacg agggcagcac cgtggagaag accgtggccc ccaccgagtg cagc 654

SEQ ID NO:107

Q S V V T Q P P S V S V A P G Q T A R I T C G G N N I G S K S V H W Y Q Q K
P G Q A P V L V V Y D D S D R P S G I P E R F S G S N S G N T A T L T I S R
V E A G D E A D Y Y C Q V W D S S S D H Y V F G T G T K V T V L G A A A G Q
P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V T V
A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P E Q
W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:108

actgtgttga cacagccgcc ctcagtgtct ggggccccag ggcagagggt caccatctcc 60
tgcactggga gcagctccaa catcggggca ggttatgatg tacactggta ccagcagctt 120
ccaggaacag cccccaaact cctcatctat ggtaacagca atcggccctc aggggtccct 180
gaccgattct ctggctccaa gtctggcacg tcagccaccc tgggcatcac cggactccag 240
actggggacg aggccgatta ttactgcgga acatgggata gcagcctgag tgcttatgtc 300
ttcggaactg ggaccaaggt caccgtccta ggtgcggccg caggccagcc caaggccgct 360
cccagcgtga ccctgttccc ccctcctcc gaggagctgc aggccaacaa ggccaccctg 420
gtgtgcctca tcagcgactt ctaccctggc gccgtgaccg tggcctggaa ggccgacagc 480
agccccgtga aggccggcgt ggagaccacc acccccagca agcagagcaa caacaagtac 540
gccgccagca gctacctgag cctcacccc gagcagtgga agagccaccg gagctacagc 600
tgccaggtga cccacgaggg cagcaccgtg gagaagaccg tggcccccac cgagtgcagc 660

SEQ ID NO:109

T V L T Q P P S V S G A P G Q R V T I S C T G S S S N I G A G Y D V H W Y Q
Q L P G T A P K L L I Y G N S N R P S G V P D R F S G S K S G T S A T L G I
T G L Q T G D E A D Y Y C G T W D S S L S A Y V F G T G T K V T V L G A A A
G Q P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V
T V A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P
E Q W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:110

M E K I V L L F A I V S L V K S D Q I C I G Y H A N N S T E Q V D T I M E K
N V T V T H A Q D I L E K K H N G K L C D L D G V K P L I L R D C S V A G W
L L G N P M C D E F I N V P E W S Y I V E K A N P V N D L C Y P G D F N D Y
E E L K H L L S R I N H F E K I Q I I P K S S W S S H E A S L G V S S A C P
Y Q G K S S F F R N V V W L I K K N S T Y P T I K R S Y N N T N Q E D L L V
L W G I H H P N D A A E Q T K L Y Q N P T T Y I S V G T S T L N Q R L V P R
I A T R S K V N G Q S G R M E F F W T I L K P N D A I N F E S N G N F I A P
E Y A Y K I V K K G D S T I M K S E L E Y G N C N T K C Q T P M G A I N S S
M P F H N I H P L T I G E C P K Y V K S N R L V L A T G L R N S P Q R E R R
R K K R G L F G A I A G F I E G G W Q G M V D G W Y G Y H H S N E Q G S G Y
A A D K E S T Q K A I D G V T N K V N S I I D K M N T Q F E A V G R E F N N
L E R R I E N L N K K M E D G F L D V W T Y N A E L L V L M E N E R T L D F
H D S N V K N L Y D K V R L Q L R D N A K E L G N G C F E F Y H K C D N E C
M E S V R N G T Y D Y P Q Y S E E A R L K R E E I S G V K L E S I G I Y Q I
L S I Y S T V A S S L A L A I M V A G L S L W M C S N G S L Q C R

SEQ ID NO:111

M E K I V L L F A I V S L V K S D Q I C I G Y H A N N S T E Q V D T I M E K
N V T V T H A Q D I L E K T H N G K L C D L D G V K P L I L R D C S V A G W
L L G N P M C D E F I N V P E W S Y I V E K A N P V N D L C Y P G D F N D Y
E E L K H L L S R I N H F E K I Q I I P K S S W S S H E A S L G V S S A C P
Y Q G K S S F F R N V V W L I K K N S T Y P T I K R S Y N N T N Q E D L L V
L W G I H H P N D A A E Q T K L Y Q N P T T Y I S V G T S T L N Q R L V P R
I A T R S K V N G Q S G R M E F F W T I L K P N D A I N F E S N G N F I A P
E Y A Y K I V K K G D S T I M K S E L E Y G N C N T K C Q T P M G A I N S S
M P F H N I H P L T I G E C P K Y V K S N R L V L A T G L R N S P Q R E R R

RKKRGLFGAIAGFIEGGWQGMVDGWYGYHHSNEQGSGY
AADKESTQKAIDGVTNKVNSIIDKMNTQFEAVGREFNN
LERRIENLNKKMEDGFLDVWTYNAELLVLMENERTLDF
HDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNEC
MESVRNGTYDYPQYSEEARLKREEISGVKLESIGIYQI
LSIYSTVASSLALAIMVAGLSLWMCSNGSLQCR

SEQ ID NO:112

MEKIVLLLAIVSLVKSDQICIGYHANNSTEQVDTIMEK
NVTVTHAQDILEKTHNGKLCDLDGVKPLILRDCSVAGW
LLGNPMCDEFINVPEWSYIVEKANPANDLCYPGNFNDY
EELKHLLSRINHFEKIQIIPKSSWSDHEASSGVSSACP
YQGKSSFFRNVVWLIKKNSSYPTIKRSYNNTNQEDLLV
LWGIHHPNDAAEQTRLYQNPTTYISVGTSTLNQRLVPK
IATRSKVNGQSGRMEFFWTILKPNDAINFESNGNFIAP
EYAYKIVKKGDSAIMKSELEYGNCNTKCQTPMGAINSS
MPFHNIHPLTIGECPKYVKSNRLVLATGLRNSPQRERR
RKKRGLFGAIAGFIEGGWQGMVDGWYGYHHSNEQGSGY
AADKESTQKAIDGVTNKVNSIIDKMNTQFEAVGREFNN
LERRIENLNKKMEDGFLDVWTYNAELLVLMENERTLDF
HDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNEC
MESVRNGTYDYPQYSEEARLKREEISGVKLESIGIYQI
LSIYSTVASSLALAIMVAGLSLWMCSNGSLQCR

SEQ ID NO:113

MEKIVLLFAIVSLVKSDQICIGYHANNSTEQVDTIMEK
NVTVTHAQDILEKTHNGKLCDLDGVKPLILRDCSVAGW
LLGNPMCDEFINVPEWSYIVEKANPVNDLCYPGDFNDY
EELKHLLSRINHFEKIQIIPKSSWSSHEASLGVSSACP
YQGKSSFFRNVVWLIKKNSTYPTIKRSYNNTNQEDLLV
LWGIHHPNDAAEQTKLYQNPTTYISVGTSTLNQRLVPR
IATRSKVNGQSGRMEFFWTILKPNDAINFESNGNFIAP
EYAYKIVKKGDSTIMKSELEYGNCNTKCQTPMGAINSS
MPFHNIHPLTIGECPKYVKSNRLVLATGLRNSPQRERR
RKKRGLFGAIAGFIEGGWQGMVDGWYGYHHSNEQGSGY
AADKESTQKAIDGVTNKVNSIIDKMNTQFEAVGREFNN
LERRIENLNKKMEDGFLDVWTYNAELLVLMENERTLDF
HDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNEC
MESVRNGTYDYPQYSEEARLKREEISGVKLESIGIYQI
QHSGGRSSLEGPRFEQKLISEEDLNMHTGHHHHHH

SEQ ID NO:114

MEKIVLLLAIVSLVKSDQICIGYHANNSTEQVDTIMEK
NVTVTHAQDILEKTHNGKLCDLDGVKPLILRDCSVAGW
LLGNPMCDEFINVPEWSYIVEKANPANDLCYPGNFNDY
EELKHLLSRINHFEKIQIIPKSSWSDHEASSGVSSACP
YQGKSSFFRNVVWLIKKNSSYPTIKRSYNNTNQEDLLV
LWGIHHPNDAAEQTRLYQNPTTYISVGTSTLNQRLVPK
IATRSKVNGQSGRMEFFWTILKPNDAINFESNGNFIAP
EYAYKIVKKGDSAIMKSELEYGNCNTKCQTPMGAINSS
MPFHNIHPLTIGECPKYVKSNRLVLATGLRNSPQRERR
RKKRGLFGAIAGFIEGGWQGMVDGWYGYHHSNEQGSGY
AADKESTQKAIDGVTNKVNSIIDKMNTQFEAVGREFNN
LERRIENLNKKMEDGFLDVWTYNAELLVLMENERTLDF
HDSNVKNLYDKVRLQLRDNAKELGNGCFEFYHKCDNEC
MESVRNGTYDYPQYSEEARLKREEISGVKLESIGIYQI
QHSGGRSSLEGPRFEQKLISEEDLNMHTGHHHHHH

SEQ ID NO:115

gaggtgcagc tggtggagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaagtc 60
tcttgcaagg cttctggagg ccccttccgc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcctgagtg gatgggaggg atcatcccta tttttggtac aacaaaatac 180
gcaccgaagt tccagggcag agtcacgatt accgcggacg atttcgcggg cacagtttac 240
atggagctga gcagcctgcg atctgaggac acggccatgt actactgtgc gaaacatatg 300
gggtaccagg tgcgcgaaac tatggacgtc tggggcaaag ggaccacggt caccgtctcg 360
agcggtacgg gcggttcagg cggaaccggc agcggcactg gcgggtcgac gtcctatgtg 420
ctgactcagc caccctcagc gtctgggacc cccgggcaga gggtcaccat ctcttgttct 480
ggaagcacgt tcaacatcgg aagtaatgct gtagactggt accggcagct cccaggaacg 540
gcccccaaac tcctcatcta tagtaataat cagcggccct caggggtccc tgaccgattc 600
tctggctcca ggtctggcac ctcagcctcc ctggccatca gtgggctcca gtctgaggat 660
gaggctgatt attactgtgc agcatgggat gacatcctga atgttccggt attcggcgga 720
gggaccaagc tgaccgtcct aggt 744

SEQ ID NO:116

E V Q L V E S G A E V K K P G S S V K V S C K A S G G P F R S Y A I S W V R
Q A P G Q G P E W M G G I I P I F G T T K Y A P K F Q G R V T I T A D D F A
G T V Y M E L S S L R S E D T A M Y Y C A K H M G Y Q V R E T M D V W G K G
T T V T V S S G T G G S G G T G S G T G G S T S Y V L T Q P P S A S G T P G
Q R V T I S C S G S T F N I G S N A V D W Y R Q L P G T A P K L L I Y S N N
Q R P S G V P D R F S G S R S G T S A S L A I S G L Q S E D E A D Y Y C A A
W D D I L N V P V F G G G T K L T V L G

SEQ ID NO:117

caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaagtc 60
tcttgcaagg cttctggagg ccccttccgc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcctgagtg gatgggaggg atcatcccta tttttggtac aacaaaatac 180
gcaccgaagt tccagggcag agtcacgatt accgcggacg atttcgcggg cacagtttac 240
atggagctga gcagcctgcg atctgaggac acggccatgt actactgtgc gaaacatatg 300
gggtaccagg tgcgcgaaac tatggacgtc tggggcaaag ggaccacggt caccgtctcg 360
agcggtacgg gcggttcagg cggaaccggc agcggcactg gcgggtcgac gcagtctgcc 420
ctgactcagc ctgccgccgt gtctgggtct cctggacagt cgatcaccat ctcctgcact 480
ggaaccagca gtgacgttgg tggttataac tatgtctcct ggtaccaaca gcacccaggc 540
aaagccccca aactcatgat ttatgaggtc agtaatcggc cctcaggggt ttctaatcgc 600
ttctctggct ccaagtctgg caacacggcc tccctgacca tctctgggct ccaggctgag 660
gacgaggctg attattactg cagctcatat acaagcagca gcacttatgt cttcggaact 720
gggaccaagg tcaccgtcct aggt 744

SEQ ID NO:118

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G P F R S Y A I S W V R
Q A P G Q G P E W M G G I I P I F G T T K Y A P K F Q G R V T I T A D D F A
G T V Y M E L S S L R S E D T A M Y Y C A K H M G Y Q V R E T M D V W G K G
T T V T V S S G T G G S G G T G S G T G G S T Q S A L T Q P A A V S G S P G
Q S I T I S C T G T S S D V G G Y N Y V S W Y Q Q H P G K A P K L M I Y E V
S N R P S G V S N R F S G S K S G N T A S L T I S G L Q A E D E A D Y Y C S
S Y T S S S T Y V F G T G T K V T V L G

SEQ ID NO:119

gaggtgcagc tggtggagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaagtc 60
tcttgcaagg cttctggagg ccccttccgc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcctgagtg gatgggaggg atcatcccta tttttggtac aacaaaatac 180
gcaccgaagt tccagggcag agtcacgatt accgcggacg atttcgcggg cacagtttac 240
atggagctga gcagcctgcg atctgaggac acggccatgt actactgtgc gaaacatatg 300
gggtaccagg tgcgcgaaac tatggacgtc tggggcaaag ggaccacggt caccgtctcg 360
agcggtacgg gcggttcagg cggaaccggc agcggcactg gcgggtcgac gtcctatgtg 420

ctgactcagc caccctcagt ctctgggacc cccgggcaga gggtcaccat ctcttgctct 480
ggaagccgct ccaacgtcgg agataattct gtatattggt atcaacacgt cccagaaatg 540
gcccccaaac tcctcgtcta taagaatact caacggccct caggagtccc tgcccggttt 600
tccggctcca agtctggcac ttcagcctcc ctggccatca ttggcctcca gtccggcgat 660
gaggctgatt attattgtgt ggcatgggat gacagcgtag atggctatgt cttcggatct 720
gggaccaagg tcaccgtcct aggt 744

SEQ ID NO:120

E V Q L V E S G A E V K K P G S S V K V S C K A S G G P F R S Y A I S W V R
Q A P G Q G P E W M G G I I P I F G T T K Y A P K F Q G R V T I T A D D F A
G T V Y M E L S S L R S E D T A M Y Y C A K H M G Y Q V R E T M D V W G K G
T T V T V S S G T G G S G G T G S G T G G S T S Y V L T Q P P S V S G T P G
Q R V T I S C S G S R S N V G D N S V Y W Y Q H V P E M A P K L L V Y K N T
Q R P S G V P A R F S G S K S G T S A S L A I I G L Q S G D E A D Y Y C V A
W D D S V D G Y V F G S G T K V T V L G

SEQ ID NO:121

gaggtgcagc tggtggagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaagtc 60
tcttgcaagg cttctggagg ccccttccgc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcctgagtg gatgggaggg atcatcccta tttttggtac aacaaaatac 180
gcaccgaagt tccagggcag agtcacgatt accgcggacg atttcgcggg cacagtttac 240
atggagctga gcagcctgcg atctgaggac acggccatgt actactgtgc gaaacatatg 300
gggtaccagg tgcgcgaaac tatggacgtc tggggcaaag ggaccacggt caccgtctcg 360
agcggtacgg gcggttcagg cggaaccggc agcggcactg gcgggtcgac gcagtctgtg 420
ttgacgcagc cgccctcagt gtctgcggcc ccaggacaga aggtcaccat ctcctgctct 480
ggaagcagct ccaacattgg gaatgattat gtatcctggt accagcagct cccaggaaca 540
gcccccaaac tcctcattta tgacaataat aagcgaccct cagggattcc tgaccgattc 600
tctggctcca agtctggcac gtcagccacc ctgggcatca ccggactcca gactggggac 660
gaggccaact attactgcgc aacatgggat cgccgcccga ctgcttatgt tgtcttcggc 720
ggagggacca agctgaccgt cctaggt 747

SEQ ID NO:122

E V Q L V E S G A E V K K P G S S V K V S C K A S G G P F R S Y A I S W V R
Q A P G Q G P E W M G G I I P I F G T T K Y A P K F Q G R V T I T A D D F A
G T V Y M E L S S L R S E D T A M Y Y C A K H M G Y Q V R E T M D V W G K G
T T V T V S S G T G G S G G T G S G T G G S T Q S V L T Q P P S V S A A P G
Q K V T I S C S G S S S N I G N D Y V S W Y Q Q L P G T A P K L L I Y D N N
K R P S G I P D R F S G S K S G T S A T L G I T G L Q T G D E A N Y Y C A T
W D R R P T A Y V V F G G G T K L T V L G

SEQ ID NO:123

caggtacagc tgcagcagtc aggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg tttccggagt cattttcagc ggcagtgcga tcagctgggt gcgacaggcc 120
cctggacaag gccttgagtg gatgggaggg atcagccctc tctttggcac aacaaattac 180
gcacaaaagt tccagggcag agtcacgatt accgcggacc aatccacgaa cacaacctac 240
atggaggtga acagcctgag atatgaggac acggccgtgt atttctgtgc gcgaggtcca 300
aaatattaca gtgagtacat ggacgtctgg ggcaaaggga ccacggtcac cgtctcgagc 360
ggtacgggcg gttcaggcgg aaccggcagc ggcactggcg ggtcgacgga catccagatg 420
acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccgg 480
gcgagtcagg gcattagcag ttatttagcc tggtatcagc agaagccagg gaaagttcct 540
acactcctga tctatgatgc atccactttg cgatcagggg tcccatctcg cttcagtggc 600
agtggatctg cgacagattt cactctcacc atcagcagcc tgcagcctga agatgttgca 660
acttattact gtcaaaggta taacagtgcc cccccgatca ccttcggcca agggacacga 720
ctggagatta aacgt 735

SEQ ID NO:124

Q V Q L Q Q S G A E V K K P G S S V K V S C K V S G V I F S G S A I S W V R
Q A P G Q G L E W M G G I S P L F G T T N Y A Q K F Q G R V T I T A D Q S T
N T T Y M E V N S L R Y E D T A V Y F C A R G P K Y Y S E Y M D V W G K G T
T V T V S S G T G G S G G T G S G T G G S T D I Q M T Q S P S S L S A S V G
D R V T I T C R A S Q G I S S Y L A W Y Q Q K P G K V P T L L I Y D A S T L
R S G V P S R F S G S G S A T D F T L T I S S L Q P E D V A T Y Y C Q R Y N
S A P P I T F G Q G T R L E I K R

SEQ ID NO:125

caggtccagc tggtacagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcagt agttatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggagga atcatgggta tgtttggcac aactaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aattcacgag cgcagcctac 240
atggagctga ggagcctgag atctgaggac acggccgtct actactgtgc gaggtctagt 300
ggttattacc ccgaatactt ccaggactgg ggccagggca ccctggtcac cgtctcgagc 360
ggtacgggcg gttcaggcgg aaccggcagc ggcactggcg ggtcgacgca gtctgtgctg 420
actcagccac cctcagagtc cgtgtcccca ggacagacag ccagcgtcac ctgctctgga 480
cataaattgg gggataaata tgtttcgtgg tatcagcaga agccaggcca gtcccctgta 540
ttactcatct atcaagataa caggcggccc tcagggatcc ctgagcgatt cataggctcc 600
aactctggga acacagccac tctgaccatc agcgggaccc aggctctgga tgaggctgac 660
tattactgtc aggcgtggga cagcagcact gcggttttcg gcggagggac caagctgacc 720
gtcctaggt 729

SEQ ID NO:126

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G T F S S Y A I S W V R
Q A P G Q G L E W M G G I M G M F G T T N Y A Q K F Q G R V T I T A D E F T
S A A Y M E L R S L R S E D T A V Y Y C A R S S G Y Y P E Y F Q D W G Q G T
L V T V S S G T G G S G G T G S G T G G S T Q S V L T Q P P S E S V S P G Q
T A S V T C S G H K L G D K Y V S W Y Q Q K P G Q S P V L L I Y Q D N R R P
S G I P E R F I G S N S G N T A T L T I S G T Q A L D E A D Y Y C Q A W D S
S T A V F G G G T K L T V L G

SEQ ID NO:127

caggtccagc tggtgcagtc tgggggaggc ctggtcaagc ctgggggggtc cctgagactc 60
tcctgtgcag cctctggatt caccttcagt agctatagca tgaactgggt ccgccaggct 120
ccagggaagg ggctggagtg ggtctcatcc attagtagta gtagtagtta catatactac 180
gtagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctcactgtat 240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaggtggt 300
gggagctacg gggcctacga aggctttgac tactggggcc agggcaccct ggtcaccgtc 360
tcgagcggta cgggcggttc aggcggaacc ggcagcggca ctggcgggtc gacggaaatt 420
gtgctgactc agtctccagg caccctgtct ttgtctccag gggaaagagc caccctctcc 480
tgcagggcca gtcagcgtgt tagcagctac ttagcctggt accaacagaa acctggccag 540
gctcccaggc tcctcatcta tggtgcatcc accagggccg ctggcatccc agacaggttc 600
agtggcagtg ggtctgggac agacttcact ctcaccatca gcagactgga gcctgaagat 660
tctgcagtgt attactgtca gcagtatggt aggacaccgc tcactttcgg cggagggacc 720
aaggtggaga tcaaacgt 738

SEQ ID NO:128

Q V Q L V Q S G G G L V K P G G S L R L S C A A S G F T F S S Y S M N W V R
Q A P G K G L E W V S S I S S S S S S Y I Y Y V D S V K G R F T I S R D N A K
N S L Y L Q M N S L R A E D T A V Y Y C A R G G G S Y G A Y E G F D Y W G Q
G T L V T V S S G T G G S G G T G S G T G G S T E I V L T Q S P G T L S L S
P G E R A T L S C R A S Q R V S S Y L A W Y Q Q K P G Q A P R L L I Y G A S
T R A A G I P D R F S G S G S G T D F T L T I S R L E P E D S A V Y Y C Q Q
Y G R T P L T F G G G T K V E I K R

SEQ ID NO:129

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SEQ ID NO:130

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T T V T V S S G T G G S G G T G S G T G G S T S Y V L T Q P P S V S V A P G
Q T A R I T C G G N N I G S K S V H W Y Q Q K P G Q A P V L V V Y D D S D R
P S G I P E R F S G S N S G N T A T L T I S R V E A G D E A D Y Y C Q V W D
S S S D H A V F G G G T Q L T V L G

SEQ ID NO:131

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SEQ ID NO:132

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G T V Y M E L S S L R S E D T A M Y Y C A K H M G Y Q V R E T M D V W G K G
T T V T V S S G T G G S G G T G S G T G G S T S Y V L T Q P P S A S G T P G
Q R V T I S C S G S S S N I G S N Y V Y W Y Q Q L P G T A P K L L I Y R D G
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SEQ ID NO:133

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gtggagatca aacgt 735

SEQ ID NO:134
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S T A Y M E L S S L R S E D T A V Y Y C A R S S G Y Y P A Y L P H W G Q G T
L V T V S S G T G G S G G T G S G T G G S T E I V L T Q S P G T L S L S P G
E R A T L S C R A S Q S V S S S Y L A W Y Q Q K P G Q A P R L L I Y G A S S
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G S S P R T F G G G T K V E I K R

SEQ ID NO:135
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SEQ ID NO:136
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S T A Y M E V S S L R S E D T A V Y Y C A R G D K G I Y Y Y Y M D V W G K G
T T V T V S S G T G G S G G T G S G T G G S T Q S A L T Q P A S V S G S P G
Q S I T I S C T G T S S D V G G Y N Y V S W Y Q Q H P G K A P K L M I Y E V
S N R P S G V S N R F S G S K S G N T A S L T I S G L Q A E D E A D Y Y C S
S Y T S S S T L V F G T G T K V T V L G

SEQ ID NO:137
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SEQ ID NO:138
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S T A Y M E L S S L R S E D T A V Y Y C A R G N Y Y Y E S S L D Y W G Q G T
L V T V S S G T G G S G G T G S G T G G S T Q S V V T Q P P S V S V A P G Q
T A R I T C G G N N I G S K S V H W Y Q Q K P G Q A P V L V V Y D D S D R P
S G I P E R F S G S N S G N T A T L T I S R V E A G D E A D Y Y C Q V W D S
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SEQ ID NO:139

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SEQ ID NO:140

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S T V Y M E L S G L R S E D T A M Y Y C A R I P H Y N F G S G S Y F D Y W G
Q G T L V T V S S G T G G S G G T G S G T G G S T T V L T Q P P S V S G A P
G Q R V T I S C T G S S S N I G A G Y D V H W Y Q Q L P G T A P K L L I Y G
N S N R P S G V P D R F S G S K S G T S A T L G I T G L Q T G D E A D Y Y C
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SEQ ID NO:141

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SEQ ID NO:212

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SEQ ID NO:213

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SEQ ID NO:214

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SEQ ID NO:215

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S V T I S C T G T S S D V G G Y N Y V S W Y Q Q H P G K A P K L M I Y D V S
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SEQ ID NO:216

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SEQ ID NO:217

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SEQ ID NO:218

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SEQ ID NO:219

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SEQ ID NO:220

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cctggacaag ggcttgagtg gatgggaggg atcatcgcta tcttcggaac agcaaactac 180
gcacagaagt tccagggcag aatcacgatt accgcggacg aatccacgag tacagcctac 240
atggagctga gcagcctgag atctgaggac acggccgtgt atttctgtgc gagaggcagt 300
ggttatcata tatcgacacc ctttgacaac tggggccagg gaaccctggt caccgtctcg 360
agcggtacgg gcggttcagg cggaaccggc agcggcactg gcgggtcgac gtcctatgtg 420
ctgactcagc caccctcggt gtcagtggcc ccaggacaga cggccaggat tacctgtggg 480
ggaaacaaca ttggaagtaa aggtgtgcac tggtaccagc agaagcctgg ccaggcccct 540
gtgctggtcg tctatgatga tagcgaccgg ccctcaggga tccctgagcg attctctggc 600
tccaactctg ggaacacggc caccctgacc atcagcaggg tcgaagccgg ggatgaggcc 660
gactattact gtcaggtgtg ggatagtagt agtgatcatg tggtattcgg cggagggacc 720
aagctgaccg tcctaggt 738

SEQ ID NO:221

E V Q L V E T G A E V K K P G S S V K V S C K A S G G T F R T H A I S W V R
Q A P G Q G L E W M G G I I A I F G T A N Y A Q K F Q G R I T I T A D E S T
S T A Y M E L S S L R S E D T A V Y F C A R G S G Y H I S T P F D N W G Q G
T L V T V S S G T G G S G G T G S G T G G S T S Y V L T Q P P S V S V A P G
Q T A R I T C G G N N I G S K G V H W Y Q Q K P G Q A P V L V V Y D D S D R
P S G I P E R F S G S N S G N T A T L T I S R V E A G D E A D Y Y C Q V W D
S S S D H V V F G G G T K L T V L G

SEQ ID NO:222

gaggtgcagc tggtggagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggaca catcttcagc ggctatgcaa tcagttgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcccta tctttggtac aacaaactac 180
gcacagaagt tccagggcag agtcacgatt accgcggacc aatccacgag cacagcctac 240
atggacctga gcaacttgag atctgaggac acggccgtct attactgtgc gagagtgaaa 300
gatggatatt gtactcttac cagctgccct gtcggctggt acttcgatct ctggggccgt 360
ggcaccctgg tcactgtctc gagcggtacg ggcggttcag gcggaaccgg cagcggcact 420
ggcgggtcga cggaaattgt gatgacgcag tctccaggca ccctgtcttt gtctccaggg 480
gaaagagcca ccctctcgtg cagggccagt cagagtgtta gcagcagcta cttagcctgg 540
taccagcaga aacctggcca ggctcccagg ctcctcatct ttggtgcctc cagcagggcc 600
actggcatcc cagacaggtt cagtggcagt gggtctggga cagacttcac tctcaccatc 660
agcagactgg agcctgaaga ttttgcagtg tattactgtc agcagtatgg tagctcactc 720
actttcggcg gagggaccaa gctggagatc aaacgt 756

SEQ ID NO:223

E V Q L V E S G A E V K K P G S S V K V S C K A S G H I F S G Y A I S W V R
Q A P G Q G L E W M G G I I P I F G T T N Y A Q K F Q G R V T I T A D Q S T
S T A Y M D L S N L R S E D T A V Y Y C A R V K D G Y C T L T S C P V G W Y
F D L W G R G T L V T V S S G T G G S G G T G S G T G G S T E I V M T Q S P
G T L S L S P G E R A T L S C R A S Q S V S S S Y L A W Y Q Q K P G Q A P R
L L I F G A S S R A T G I P D R F S G S G S G T D F T L T I S R L E P E D F
A V Y Y C Q Q Y G S S L T F G G G T K L E I K R

SEQ ID NO:224

gaggtccagc tggtacagtc tggggctgag gttaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg catcttcaga agcaattcta tcagttgggt gcgacaggcc 120
cctgggcaag ggcttgagtg gatgggaggg atcttcgctc ttttcggaac aacagactac 180
gcgcagaagt tccagggcag agtcacgatt accgcggacg aatcttcgac cacagtctac 240
ctggagctga gtagcctgac atctgaggac acggccgttt attactgtgc gagaggcagt 300
ggctacacca cacgcaacta ctttgactac tggggccagg gcaccctggt caccgtctcg 360
agcggtacgg gcggttcagg cggaaccggc agcggcactg gcgggtcgac ggaaattgtg 420
ctgactcagt ctccaggcac cctgtctttg tctccagggg aaagagccac actctcctgc 480
agggccagtc agagtgttag cagcaactac ttaggctggt accagcagaa acctggccag 540
gctcccaggc tcctgatcta tggtgcatcc agcagggcca gtggcatccc agacaggttc 600
agtggcggtg ggtctgggac agacttcact ctcaccatca gcagactgga gcctgaagat 660
tttgcagtgt attactgtca gcagtatggt agctcacccc tcactttcgg cggagggacc 720
aaggtggaga tcaaacgt 738

SEQ ID NO:225

E V Q L V Q S G A E V K K P G S S V K V S C K A S G G I F R S N S I S W V R
Q A P G Q G L E W M G G I F A L F G T T D Y A Q K F Q G R V T I T A D E S S
T T V Y L E L S S L T S E D T A V Y Y C A R G S G Y T T R N Y F D Y W G Q G
T L V T V S S G T G G S G G T G S G T G G S T E I V L T Q S P G T L S L S P
G E R A T L S C R A S Q S V S S N Y L G W Y Q Q K P G Q A P R L L I Y G A S
S R A S G I P D R F S G G G S G T D F T L T I S R L E P E D F A V Y Y C Q Q
Y G S S P L T F G G G T K V E I K R

SEQ ID NO:226

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtaaaggtc 60
tcctgcaagg cttctggagg ccccttccgc aattttgcta tcaactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcgctg tctttgggac gacaaagtac 180
gcacataagt tccagggcag agtcaccatc accgcggacg actccacaaa tacagcttac 240
atggagctgg gcagcctgaa atctgaggac acggccgtgt attactgtgc gagaggtccc 300
cactactact cctcctacat ggacgtctgg ggcgaaggga ccacggtcac cgtctcgagc 360
ggtacgggcg gttcaggcgg aaccggcagc ggcactggcg ggtcgacgga catccagttg 420
acccagtctc catcctccct gtctgcatct gtaggagaca gagtcaccat cacttgccgg 480

gcgagtcagg gcattagcac ttatttagcc tggtatcagc agaaacccgg gaaagttcct 540
aaactcctga tctatgctgc atccactttg caatcagggg tcccatctcg gttcagtggc 600
agtggatctg ggacagattt cactctcacc atcagcagcc tgcagcctga agatgttgca 660
acttattact gtcaaaagta taacagtgcc ccttctttcg gccctgggac caaagtggat 720
atcaaacgt 729

SEQ ID NO:227
Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G P F R N F A I N W V R
Q A P G Q G L E W M G G I I A V F G T T K Y A H K F Q G R V T I T A D D S T
N T A Y M E L G S L K S E D T A V Y Y C A R G P H Y Y S S Y M D V W G E G T
T V T V S S G T G G S G G T G S G T G G S T D I Q L T Q S P S S L S A S V G
D R V T I T C R A S Q G I S T Y L A W Y Q Q K P G K V P K L L I Y A A S T L
Q S G V P S R F S G S G S G T D F T L T I S S L Q P E D V A T Y Y C Q K Y N
S A P S F G P G T K V D I K R

SEQ ID NO:228
gaggtgcagc tggtggagac tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
ccctgcaaat cttctggaag ccccttcagg agtaatgctg tcagctgggt gcgacaggcc 120
cccggacaag ggcttgagtg ggtgggagga atcctcggtg tctttggttc accaagctac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccaccaa cacagtccac 240
atggagctga gaggtttgag atctgaggac acggccgtgt attattgtgc gagaggtcct 300
acctactact actcctacat ggacgtctgg ggcaaaggga ccacggtcac cgtctcgagc 360
ggtacgggcg gttcaggcgg aaccggcagc ggcactggcg ggtcgacgtc ctatgtgctg 420
actcagccac cctcggagtc agtggcccca ggacagacgg ccaggattac ctgtggggga 480
aataacattg gaagaaatag tgtgcactgg tatcagcaga agccaggcca ggcccctgtg 540
ctggtcgtgt atgatgatag cgaccggccc tcagggatcc ctgagcgatt ttctggctcc 600
aagtctggga acacggccac cctgattatc agcagggtcg aagtcgggga tgaggccgac 660
tactactgtc aggtgtggca tagtagtagt gatcattatg tcttcggaac tgggaccaag 720
gtcaccgtcc taggt 735

SEQ ID NO:229
E V Q L V E T G A E V K K P G S S V K V P C K S S G S P F R S N A V S W V R
Q A P G Q G L E W V G G I L G V F G S P S Y A Q K F Q G R V T I T A D E S T
N T V H M E L R G L R S E D T A V Y Y C A R G P T Y Y Y S Y M D V W G K G T
T V T V S S G T G G S G G T G S G T G G S T S Y V L T Q P P S E S V A P G Q
T A R I T C G G N N I G R N S V H W Y Q Q K P G Q A P V L V V Y D D S D R P
S G I P E R F S G S K S G N T A T L I I S R V E V G D E A D Y Y C Q V W H S
S S D H Y V F G T G T K V T V L G

SEQ ID NO:230
cagatgcagc tggtacaatc tggagctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcttcggta tgtttgggac agcaaactac 180
gcgcagaagt tccagggcag agtcacgatt accgcggacg aattcacgag cgcggcctac 240
atggagctga gcagcctggg atctgaggac acggccatgt attactgtgc gaggtctagt 300
ggttattacc cccaatactt ccaggactgg ggccagggca ccctggtcac cgtctcgagc 360
ggtacgggcg gttcaggcgg aaccggcagc ggcactggcg ggtcgacgga aattgtgatg 420
acacagtctc caggcaccct gtctttgtct ccagggcaaa gagccaccct ctcctgcagg 480
gccagtcaga gtgttagcag cagctactta gcctggtacc agcagaaacc tggccaggct 540
cccagactcc tcatgtatgg tgcatccagc agggccactg gcatcccaga caggttcagt 600
ggcagtgggt ctgggacaga cttcactctc accatcagca gactggagcc tgaagatttt 660
gcagtgtatt actgtcagca gtatggtagc tcatcgctca ctttcggcgg agggaccaag 720
ctggagatca aacgt 735

SEQ ID NO:231
Q M Q L V Q S G A E V K K P G S S V K V S C K A S G G T F S S Y A I S W V R
Q A P G Q G L E W M G G I F G M F G T A N Y A Q K F Q G R V T I T A D E F T

S A A Y M E L S S L G S E D T A M Y Y C A R S S G Y Y P Q Y F Q D W G Q G T
L V T V S S G T G G S G G T G S G T G G S T E I V M T Q S P G T L S L S P G
Q R A T L S C R A S Q S V S S S Y L A W Y Q Q K P G Q A P R L L M Y G A S S
R A T G I P D R F S G S G S G T D F T L T I S R L E P E D F A V Y Y C Q Q Y
G S S S L T F G G G T K L E I K R

SEQ ID NO:232

gaggtgcagc tggtggagtc cggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg catcttcaac agttatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggc atcatcgcta tctttcatac accaaagtac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgaa cacagcctac 240
atggaactga gaagcctgaa atctgaggac acggccctgt attactgtgc gagagggtcc 300
acttacgatt tttcgagtgg ccttgactac tggggccagg gaaccctggt caccgtctcg 360
agcggtacgg gcggttcagg cggaaccggc agcggcactg gcgggtcgac gcaggcaggg 420
ctgactcagc caccctcggt gtcagtggcc ccaggacaga cggccaggat tacctgtggg 480
ggaaacaaca ttggaagtaa aagtgtgcac tggtaccagc agaagccagg ccaggcccct 540
gtcctagtcg tctatgatga tagcgaccgg ccctcaggga tccctgagcg attctctggc 600
tccaactctg ggaacacggc caccctgacc atcagcaggg tcgaagccgg ggatgaggcc 660
gactattact gtcaggtgtg ggatagtagt agtgatcatg tggtattcgg cggagggacc 720
aagctgaccg tcctaggt 738

SEQ ID NO:233

E V Q L V E S G A E V K K P G S S V K V S C K A S G G I F N S Y A I S W V R
Q A P G Q G L E W M G G I I A I F H T P K Y A Q K F Q G R V T I T A D E S T
N T A Y M E L R S L K S E D T A L Y Y C A R G S T Y D F S S G L D Y W G Q G
T L V T V S S G T G G S G G T G S G T G G S T Q A G L T Q P P S V S V A P G
Q T A R I T C G G N N I G S K S V H W Y Q Q K P G Q A P V L V V Y D D S D R
P S G I P E R F S G S N S G N T A T L T I S R V E A G D E A D Y Y C Q V W D
S S S D H V V F G G G T K L T V L G

SEQ ID NO:234

caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cttcttcagc agctatgcta tcagctgggt gcgccaggcc 120
cctggacaag gacttgagtg gatgggggg gtcatcccta tctttcgtac agcaaactac 180
gcacagaact tccagggcag agtcaccatt accgcggacg aattcacatc gtatatggag 240
ctgagcagcc tgagatctga cgacacggcc gtgtattact gtgcgaggtt gaattaccat 300
gattcgggga cttattataa cgccccccgg ggctggttcg acccctgggg ccagggaacc 360
ctggtcaccg tctcgagcgg tacgggcggt tcaggcggaa ccggcagcgg cactggcggg 420
tcgacggaca tccagatgac ccagtctcca gactccctgg ctgtgtctct gggcgagaag 480
gccaccatca actgcaagtc cagccagagt attttaaaca gctccaacaa taagaactac 540
ttagcttggt accagcagaa accaggacag cctcctaagc tgctcattta ctgggcatct 600
acccgggaat ccggggtccc tgaccgattc agtggcagcg ggtctgggac agatttcact 660
ctcaccatca gcagcctgca ggctgaagat gtggcagttt attactgtca gcaatattat 720
agtagtccgc cgacgttcgg ccaagggacc aaggtggaaa tcaaacgt 768

SEQ ID NO:235

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G F F S S Y A I S W V R
Q A P G Q G L E W M G G V I P I F R T A N Y A Q N F Q G R V T I T A D E F T
S Y M E L S S L R S D D T A V Y Y C A R L N Y H D S G T Y Y N A P R G W F D
P W G Q G T L V T V S S G T G G S G G T G S G T G G S T D I Q M T Q S P D S
L A V S L G E K A T I N C K S S Q S I L N S S N N K N Y L A W Y Q Q K P G Q
P P K L L I Y W A S T R E S G V P D R F S G S G S G T D F T L T I S S L Q A
E D V A V Y Y C Q Q Y Y S S P P T F G Q G T K V E I K R

SEQ ID NO:236

caggtccagc tggtgcagtc tggagctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagt caccttcagt tactatgcta tgagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggagga atcagcccta tgtttgggac aacaacctac 180
gcacagaagt tccagggcag agtcacgatt actgcggacg actccacgag tacagcctac 240
atggaggtga ggagcctgag atctgaggac acggccgtgt attactgtgc gagatcttcg 300
aattactatg atagtgtata tgactactgg ggccagggaa ccctggtcac cgtctcgagc 360
ggtacgggcg gttcaggcgg aaccggcagc ggcactggcg ggtcgacgca gtctgtcgtg 420
acgcagccgc cctcggagtc agtggcccca ggacagacgg ccaggattac ctgtggggga 480
cataacattg gaagtaatag tgtgcactgg taccagcaga agccaggcca ggcccctgtg 540
ctggtcgtgt atgataatag cgaccggccc tcagggatcc ctgagcgatt ctctggctcc 600
aactctggga acacggccac cctgaccatc agcagggtcg aagccgggga tgaggccgac 660
tattactgtc aggtgtgggg tagtagtagt gaccattatg tcttcggaac tgggaccaag 720
gtcaccgtcc taggt 735

SEQ ID NO:237

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G V T F S Y Y A M S W V R
Q A P G Q G L E W M G G I S P M F G T T T Y A Q K F Q G R V T I T A D D S T
S T A Y M E V R S L R S E D T A V Y Y C A R S S N Y Y D S V Y D Y W G Q G T
L V T V S S G T G G S G G T G S G T G G S T Q S V V T Q P P S E S V A P G Q
T A R I T C G G H N I G S N S V H W Y Q Q K P G Q A P V L V V Y D N S D R P
S G I P E R F S G S N S G N T A T L T I S R V E A G D E A D Y Y C Q V W G S
S S D H Y V F G T G T K V T V L G

SEQ ID NO:316

gaggtccagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctgggta caccttcacc ggctactatg tgtactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatggtaa cacaaactat 180
gcacagaagt tccagggcag agtcacgatt accgcggaca aatccacgag cacagcctac 240
atggagctga gcagcctgag atctgaagac acggctgtgt attactgtgc gagaagtaga 300
tccctggacg tctggggcca agggaccacg gtcaccgtct cgagtgctag caccaagggc 360
cccagcgtgt tccccctggc ccccagcagc aagagcacca gcggcggcac agccgccctg 420
ggctgcctgg tgaaggacta cttccccgag cccgtgaccg tgagctggaa cagcggcgcc 480
ttgaccagcg gcgtgcacac cttccccgcc gtgctgcaga gcagcggcct gtacagcctg 540
agcagcgtgg tgaccgtgcc cagcagcagc ctgggcaccc agacctacat ctgcaacgtg 600
aaccacaagc ccagcaacac caaggtggac aaacgcgtgg agcccaagag ctgcgacaag 660
acccacacct gccccccctg ccctgccccc gagctgctgg gcggaccctc cgtgttcctg 720
ttcccccca agcccaagga caccctcatg atcagccgga cccccgaggt gacctgcgtg 780
gtggtggacg tgagccacga ggaccccgag gtgaagttca actggtacgt ggacggcgtg 840
gaggtgcaca acgccaagac caagccccgg gaggagcagt acaacagcac ctaccgggtg 900
gtgagcgtgc tcaccgtgct gcaccaggac tggctgaacg gcaaggagta caagtgcaag 960
gtgagcaaca aggccctgcc tgcccccatc gagaagacca tcagcaaggc caagggccag 1020
ccccgggagc cccaggtgta caccctgccc cccagccggg aggagatgac caagaaccag 1080
gtgtccctca cctgtctggt gaagggcttc taccccagcg acatcgccgt ggagtgggag 1140
agcaacggcc agcccgagaa caactacaag accacccccc ctgtgctgga cagcgacggc 1200
agcttcttcc tgtacagcaa gctcaccgtg gacaagagcc ggtggcagca gggcaacgtg 1260
ttcagctgca gcgtgatgca cgaggccctg cacaaccact acacccagaa gagcctgagc 1320
ctgagccccg gcaag 1335

SEQ ID NO:317

E V Q L V Q S G A E V K K P G A S V K V S C K A S G Y T F T G Y Y V Y W V R
Q A P G Q G L E W M G W I S A Y N G N T N Y A Q K F Q G R V T I T A D K S T
S T A Y M E L S S L R S E D T A V Y Y C A R S R S L D V W G Q G T T V T V S
S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y F P E P V
T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T V P S S S
L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T C P P C P
A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V S H
E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S V L
T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q P R
E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I A V E W E

S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S R W Q Q G
N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:318

gatgttgtga tgactcagtc 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 agatgtggca gtttattact gtcagcaata ttatagtact 300
cctctcactt tcggcggagg gaccaaagtg gatatcaaac gtgcggccgc acccagcgtg 360
ttcatcttcc cccctccga cgagcagctg aagagcggca ccgccagcgt ggtgtgcctg 420
ctgaacaact tctacccccg ggaggccaag gtgcagtgga aggtggacaa cgccctgcag 480
agcggcaaca gccaggagag cgtgaccgag caggacagca aggactccac ctacagcctg 540
agcagcaccc tcaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 600
gtgacccacc agggcctgag cagccccgtg accaagagct tcaaccgggg cgagtgt 657

SEQ ID NO:319

D V V M T Q S P D S L A V S L G E R A T I N C K S S Q S V L Y S S N N K N Y
L A W Y Q Q K P G Q P P K L L I Y W A S T R E S G V P D R F S G S G S G T D
F T L T I S S L Q A E D V A V Y Y C Q Q Y Y S T P L T F G G G T K V D I K R
A A A P S V F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q
W K V D N A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D
Y E K H K V Y A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:320

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SEQ ID NO:321

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Q A P G Q G L E W M G G I I G M F G S T N Y A Q N F Q G R V T I T A D E S T
S T A Y M E L S S L R S E D T A V Y Y C A R S T G Y Y P A Y L H H W G Q G T
L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y
F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T
V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T

C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V
V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R
V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A
K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I
A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S
R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:322

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gccgccagca gctacctgag cctcacccc gagcagtgga agagccaccg gagctacagc 600
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SEQ ID NO:323

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Q Q H P G K A P K L M I Y D V S K R P S G V P D R F S G S K S G N T A S L T
I S G L Q A E D E A D Y Y C S S Y T S S S T H V F G T G T K V T V L G A A A
G Q P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V
T V A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P
E Q W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:324

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acccagaaga gcctgagcct gagccccggc aag 1353

SEQ ID NO:325

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Q A P G Q G L E W M G W I N P N S G G T N Y A Q K F Q G R V T M T R D T S I
S T A Y M E L S R L R S D D T A V Y Y C A R E G K W G P Q A A F D I W G Q G

T M V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D
Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V
T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H
T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V
V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y
R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K
A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D
I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:326

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SEQ ID NO:327

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S R L E P E D F A V Y Y C Q Q Y G S S L W T F G Q G T K V E I K R A A A P S
V F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W K V D N
A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K
V Y A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:328

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ctgagcctga gccccggcaa g 1341

SEQ ID NO:329

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N T L Y L Q M N S L R A E D T A V Y Y C A R A Y G Y T F D P W G Q G T L V T
V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y F P E
P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T V P S
S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T C P P
C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V V D V
S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R V V S
V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A K G Q
P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I A V E
W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S R W Q
Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K
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SEQ ID NO:330

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SEQ ID NO:331

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T L K I S R V E A E D V G V Y Y C M Q A L Q T P L T F G G G T K V E I K R A
A A P S V F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W
K V D N A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y
E K H K V Y A C E V T H Q G L S S P V T K S F N R G E C
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SEQ ID NO:332

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acccagaaga gcctgagcct gagccccggc aag 1353

SEQ ID NO:333

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Q A P G Q G L E W M G G I I A I F G T A N Y A Q K F Q G R I T I T A D E S T
S T A Y M E L S S L R S E D T A V Y F C A R G S G Y H I S T P F D N W G Q G
T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D
Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V
T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H
T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V
V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y
R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K
A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D
I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:334

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agcagctacc tgagcctcac ccccgagcag tggaagagcc accggagcta cagctgccag 600
gtgacccacg agggcagcac cgtggagaag accgtggccc ccaccgagtg cagc 654

SEQ ID NO:335

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P G Q A P V L V V Y D D S D R P S G I P E R F S G S N S G N T A T L T I S R
V E A G D E A D Y Y C Q V W D S S S D H V V F G G G T K L T V L G A A A G Q
P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V T V
A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P E Q
W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:336

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gatggatatt gtactcttac cagctgccct gtcggctggt acttcgatct ctggggccgt 360
ggcaccctgg tcactgtctc gagtgctagc accaagggcc ccagcgtgtt ccccctggcc 420
cccagcagca agagcaccag cggcggcaca gccgccctgg gctgcctggt gaaggactac 480
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ttccccgccg tgctgcagag cagcggcctg tacagcctga gcagcgtggt gaccgtgccc 600
agcagcagcc tgggcaccca gacctacatc tgcaacgtga accacaagcc cagcaacacc 660
aaggtggaca aacgcgtgga gcccaagagc tgcgacaaga cccacacctg ccccccctgc 720
cctgcccccg agctgctggg cggaccctcc gtgttcctgt tcccccccaa gcccaaggac 780
accctcatga tcagccggac ccccgaggtg acctgcgtgg tggtggacgt gagccacgag 840
gaccccgagg tgaagttcaa ctggtacgtg gacggcgtgg aggtgcacaa cgccaagacc 900
aagccccggg aggagcagta caacagcacc taccgggtgg tgagcgtgct caccgtgctg 960
caccaggact ggctgaacgg caaggagtac aagtgcaagg tgagcaacaa ggccctgcct 1020
gcccccatcg agaagaccat cagcaaggcc aagggccagc cccgggagcc ccaggtgtac 1080

accctgcccc ccagccggga ggagatgacc aagaaccagg tgtccctcac ctgtctggtg 1140
aagggcttct accccagcga catcgccgtg gagtgggaga gcaacggcca gcccgagaac 1200
aactacaaga ccacccccc tgtgctggac agcgacggca gcttcttcct gtacagcaag 1260
ctcaccgtgg acaagagccg gtggcagcag ggcaacgtgt tcagctgcag cgtgatgcac 1320
gaggccctgc acaaccacta cacccagaag agcctgagcc tgagccccgg caag 1374

SEQ ID NO:337

E V Q L V E S G A E V K K P G S S V K V S C K A S G H I F S G Y A I S W V R
Q A P G Q G L E W M G G I I P I F G T T N Y A Q K F Q G R V T I T A D Q S T
S T A Y M D L S N L R S E D T A V Y Y C A R V K D G Y C T L T S C P V G W Y
F D L W G R G T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A
L G C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L
Y S L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P
K S C D K T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R
T P E V T C V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E
E Q Y N S T Y R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P
I E K T I S K A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V
K G F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y
S K L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P
G K

SEQ ID NO:338

gaaattgtga tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
ctctcgtgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccaggct cctcatcttt ggtgcctcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcactcac tttcggcgga 300
gggaccaagc tggagatcaa acgtgcggcc gcacccagcg tgttcatctt ccccccctcc 360
gacgagcagc tgaagagcgg caccgccagc gtggtgtgcc tgctgaacaa cttctacccc 420
cgggaggcca aggtgcagtg gaaggtggac aacgccctgc agagcggcaa cagccaggag 480
agcgtgaccg agcaggacag caaggactcc acctacagcc tgagcagcac cctcaccctg 540
agcaaggccg actacgagaa gcacaaggtg tacgcctgcg aggtgaccca ccagggcctg 600
agcagccccg tgaccaagag cttcaaccgg ggcgagtgt 639

SEQ ID NO:339

E I V M T Q S P G T L S L S P G E R A T L S C R A S Q S V S S S Y L A W Y Q
Q K P G Q A P R L L I F G A S S R A T G I P D R F S G S G S G T D F T L T I
S R L E P E D F A V Y Y C Q Q Y G S S L T F G G G T K L E I K R A A A P S V
F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W K V D N A
L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K V
Y A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:340

gaggtccagc tggtacagtc tggggctgag gttaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg catcttcaga agcaattcta tcagttgggt gcgacaggcc 120
cctgggcaag ggcttgagtg gatgggaggg atcttcgctc ttttcggaac aacagactac 180
gcgcagaagt tccagggcag agtcacgatt accgcggacg aatcttcgac cacagtctac 240
ctggagctga gtagcctgac atctgaggac acggccgttt attactgtgc gagaggcagt 300
ggctacacca cacgcaacta ctttgactac tggggccagg gcaccctggt caccgtctcg 360
agtgctagca ccaagggccc cagcgtgttc cccctggccc ccagcagcaa gagcaccagc 420
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agctggaaca gcggcgcctt gaccagcggc gtgcacacct tccccgccgt gctgcagagc 540
agcggcctgt acagcctgag cagcgtggtg accgtgccca gcagcagcct gggcacccag 600
acctacatct gcaacgtgaa ccacaagccc agcaacacca aggtggacaa acgcgtggag 660
cccaagagct gcgacaagac ccacacctgc ccccccctgcc ctgcccccga gctgctgggc 720
ggaccctccg tgttcctgtt cccccccaag cccaaggaca ccctcatgat cagccggacc 780
cccgaggtga cctgcgtggt ggtggacgtg agccacgagg accccgaggt gaagttcaac 840

tggtacgtgg acggcgtgga ggtgcacaac gccaagacca agccccggga ggagcagtac 900
aacagcacct accgggtggt gagcgtgctc accgtgctgc accaggactg gctgaacggc 960
aaggagtaca agtgcaaggt gagcaacaag gccctgcctg cccccatcga gaagaccatc 1020
agcaaggcca agggccagcc ccgggagccc caggtgtaca ccctgccccc cagccgggag 1080
gagatgacca agaaccaggt gtccctcacc tgtctggtga agggcttcta ccccagcgac 1140
atcgccgtgg agtgggagag caacggccag cccgagaaca actacaagac cacccccccct 1200
gtgctggaca gcgacggcag cttcttcctg tacagcaagc tcaccgtgga caagagccgg 1260
tggcagcagg gcaacgtgtt cagctgcagc gtgatgcacg aggccctgca caaccactac 1320
acccagaaga gcctgagcct gagccccggc aag 1353

SEQ ID NO:341

E V Q L V Q S G A E V K K P G S S V K V S C K A S G G I F R S N S I S W V R
Q A P G Q G L E W M G G I F A L F G T T D Y A Q K F Q G R V T I T A D E S S
T T V Y L E L S S L T S E D T A V Y Y C A R G S G Y T T R N Y F D Y W G Q G
T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D
Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V
T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H
T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V
V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y
R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K
A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D
I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:342

gaaattgtgc tgactcagtc tccaggcacc ctgtctttgt ctccagggga aagagccaca 60
ctctcctgca gggccagtca gagtgttagc agcaactact taggctggta ccagcagaaa 120
cctggccagg ctcccaggct cctgatctat ggtgcatcca gcagggccag tggcatccca 180
gacaggttca gtggcggtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcaccccct cactttcggc 300
ggagggacca aggtggagat caaacgtgcg gccgcaggcc agcccaaggc cgctcccagc 360
gtgaccctgt tccccccctc ctccgaggag ctgcaggcca acaaggccac cctggtgtgc 420
ctcatcagcg acttctaccc tggcgccgtg accgtggcct ggaaggccga cagcagcccc 480
gtgaaggccg gcgtggagac caccaccccc agcaagcaga gcaacaacaa gtacgccgcc 540
agcagctacc tgagcctcac ccccgagcag tggaagagcc accggagcta cagctgccag 600
gtgacccacg agggcagcac cgtggagaag accgtggccc ccaccgagtg cagc 654

SEQ ID NO:343

E I V L T Q S P G T L S L S P G E R A T L S C R A S Q S V S S N Y L G W Y Q
Q K P G Q A P R L L I Y G A S S R A S G I P D R F S G G G S G T D F T L T I
S R L E P E D F A V Y Y C Q Q Y G S S P L T F G G G T K V E I K R A A A G Q
P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V T V
A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P E Q
W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:344

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tcctgcaagg cttctggagg ccccttccgc aattttgcta tcaactgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcatcgctg tctttgggac gacaaagtac 180
gcacataagt tccagggcag agtcaccatc accgcggacg actccacaaa tacagcttac 240
atggagctgg gcagcctgaa atctgaggac acggccgtgt attactgtgc gagaggtccc 300
cactactact cctcctacat ggacgtctgg ggcgaaggga ccacggtcac cgtctcgagt 360
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ggcctgtaca gcctgagcag cgtggtgacc gtgcccagca gcagcctggg cacccagacc 600
tacatctgca acgtgaacca caagcccagc aacaccaagg tggacaaacg cgtggagccc 660

aagagctgcg acaagaccca cacctgcccc ccctgccctg cccccgagct gctgggcgga 720
ccctccgtgt tcctgttccc ccccaagccc aaggacaccc tcatgatcag ccggaccccc 780
gaggtgacct gcgtggtggt ggacgtgagc cacgaggacc ccgaggtgaa gttcaactgg 840
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agcacctacc gggtggtgag cgtgctcacc gtgctgcacc aggactggct gaacggcaag 960
gagtacaagt gcaaggtgag caacaaggcc ctgcctgccc ccatcgagaa gaccatcagc 1020
aaggccaagg gccagccccg ggagccccag gtgtacaccc tgcccccag ccgggaggag 1080
atgaccaaga accaggtgtc cctcacctgt ctggtgaagg gcttctaccc cagcgacatc 1140
gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac cccccctgtg 1200
ctggacagcg acggcagctt cttcctgtac agcaagctca ccgtggacaa gagccggtgg 1260
cagcagggca acgtgttcag ctgcagcgtg atgcacgagg ccctgcacaa ccactacacc 1320
cagaagagcc tgagcctgag ccccggcaag 1350

SEQ ID NO:345

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G P F R N F A I N W V R
Q A P G Q G L E W M G G I I A V F G T T K Y A H K F Q G R V T I T A D D S T
N T A Y M E L G S L K S E D T A V Y Y C A R G P H Y Y S S Y M D V W G E G T
T V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y
F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T
V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T
C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V
V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R
V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A
K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I
A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S
R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:346

gacatccagt tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60
atcacttgcc gggcgagtca gggcattagc acttatttag cctggtatca gcagaaaccc 120
gggaaagttc ctaaactcct gatctatgct gcatccactt tgcaatcagg ggtcccatct 180
cggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagatgttg caacttatta ctgtcaaaag tataacagtg ccccttcttt cggccctggg 300
accaaagtgg atatcaaacg tgcggccgca cccagcgtgt tcatcttccc ccctccgac 360
gagcagctga agagcggcac cgccagcgtg gtgtgcctgc tgaacaactt ctacccccgg 420
gaggccaagg tgcagtggaa ggtggacaac gccctgcaga gcggcaacag ccaggagagc 480
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aaggccgact acgagaagca caaggtgtac gcctgcgagg tgacccacca gggcctgagc 600
agccccgtga ccaagagctt caaccggggc gagtgt 636

SEQ ID NO:347

D I Q L T Q S P S S L S A S V G D R V T I T C R A S Q G I S T Y L A W Y Q Q
K P G K V P K L L I Y A A S T L Q S G V P S R F S G S G S G T D F T L T I S
S L Q P E D V A T Y Y C Q K Y N S A P S F G P G T K V D I K R A A A P S V F
I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W K V D N A L
Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K V Y
A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:348

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ccctgcaaat cttctggaag ccccttcagg agtaatgctg tcagctgggt gcgacaggcc 120
cccggacaag ggcttgagtg ggtgggagga atcctcggtg tctttggttc accaagctac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccaccaa cacagtccac 240
atggagctga gaggtttgag atctgaggac acggccgtgt attattgtgc gagaggtcct 300
acctactact actcctacat ggacgtctgg ggcaaaggga ccacggtcac cgtctcgagt 360
gctagcacca agggccccag cgtgttcccc ctggccccca gcagcaagag caccagcggc 420
ggcacagccg ccctgggctg cctggtgaag gactacttcc ccgagcccgt gaccgtgagc 480

tggaacagcg gcgccttgac cagcggcgtg cacaccttcc ccgccgtgct gcagagcagc 540
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tacatctgca acgtgaacca caagcccagc aacaccaagg tggacaaacg cgtggagccc 660
aagagctgcg acaagaccca cacctgcccc ccctgccctg cccccgagct gctgggcgga 720
ccctccgtgt tcctgttccc ccccaagccc aaggacaccc tcatgatcag ccggacccct 780
gaggtgacct gcgtggtggt ggacgtgagc cacgaggacc ccgaggtgaa gttcaactgg 840
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agcacctacc gggtggtgag cgtgctcacc gtgctgcacc aggactggct gaacggcaag 960
gagtacaagt gcaaggtgag caacaaggcc ctgcctgccc ccatcgagaa gaccatcagc 1020
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atgaccaaga accaggtgtc cctcacctgt ctggtgaagg gcttctaccc cagcgacatc 1140
gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac ccccctgtg 1200
ctggacagcg acggcagctt cttcctgtac agcaagctca ccgtggacaa gagccggtgg 1260
cagcagggca acgtgttcag ctgcagcgtg atgcacgagg ccctgcacaa ccactacacc 1320
cagaagagcc tgagcctgag ccccggcaag 1350

SEQ ID NO:349

E V Q L V E T G A E V K K P G S S V K V P C K S S G S P F R S N A V S W V R
Q A P G Q G L E W V G G I L G V F G S P S Y A Q K F Q G R V T I T A D E S T
N T V H M E L R G L R S E D T A V Y Y C A R G P T Y Y Y S Y M D V W G K G T
T V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y
F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T
V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T
C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V
V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R
V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A
K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I
A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S
R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:350

tcctatgtgc tgactcagcc accctcggag tcagtggccc caggacagac ggccaggatt 60
acctgtgggg gaaataacat tggaagaaat agtgtgcact ggtatcagca gaagccaggc 120
caggcccctg tgctggtcgt gtatgatgat agcgaccggc cctcagggat ccctgagcga 180
ttttctggct ccaagtctgg gaacacggcc accctgatta tcagcagggt cgaagtcggg 240
gatgaggccg actactactg tcaggtgtgg catagtagta gtgatcatta tgtcttcgga 300
actgggacca aggtcaccgt cctaggtgcg gccgcaggcc agcccaaggc cgctcccagc 360
gtgaccctgt tccccccctc ctccgaggag ctgcaggcca acaaggccac cctggtgtgc 420
ctcatcagcg acttctaccc tggcgccgtg accgtggcct ggaaggccga cagcagcccc 480
gtgaaggccg gcgtggagac caccaccccc agcaagcaga gcaacaacaa gtacgccgcc 540
agcagctacc tgagcctcac ccccgagcag tggaagagcc accggagcta cagctgccag 600
gtgacccacg agggcagcac cgtggagaag accgtggccc ccaccgagtg cagc 654

SEQ ID NO:351

S Y V L T Q P P S E S V A P G Q T A R I T C G G N N I G R N S V H W Y Q Q K
P G Q A P V L V V Y D D S D R P S G I P E R F S G S K S G N T A T L I I S R
V E V G D E A D Y Y C Q V W H S S S D H Y V F G T G T K V T V L G A A A G Q
P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V T V
A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P E Q
W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:352

cagatgcagc tggtacaatc tggagctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggaggg atcttcggta tgtttgggac agcaaactac 180
gcgcagaagt tccagggcag agtcacgatt accgcggacg aattcacgag cgcggcctac 240
atggagctga gcagcctggg atctgaggac acggccatgt attactgtgc gaggtctagt 300

ggttattacc cccaatactt ccaggactgg ggccagggca ccctggtcac cgtctcgagt 360
gctagcacca agggccccag cgtgttcccc ctggccccca gcagcaagag caccagcggc 420
ggcacagccg ccctgggctg cctggtgaag gactacttcc ccgagcccgt gaccgtgagc 480
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aagagctgcg acaagaccca cacctgcccc ccctgccctg cccccgagct gctgggcgga 720
ccctccgtgt tcctgttccc ccccaagccc aaggacaccc tcatgatcag ccggacccct 780
gaggtgacct gcgtggtggt ggacgtgagc cacgaggacc ccgaggtgaa gttcaactgg 840
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gagtacaagt gcaaggtgag caacaaggcc ctgcctgccc ccatcgagaa gaccatcagc 1020
aaggccaagg gccagccccg ggagccccag gtgtacaccc tgcccccag ccgggaggag 1080
atgaccaaga accaggtgtc cctcacctgt ctggtgaagg gcttctaccc cagcgacatc 1140
gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac cccccctgtg 1200
ctggacagcg acggcagctt cttcctgtac agcaagctca ccgtggacaa gagccggtgg 1260
cagcagggca acgtgttcag ctgcagcgtg atgcacgagg ccctgcacaa ccactacacc 1320
cagaagagcc tgagcctgag ccccggcaag 1350

SEQ ID NO:353

Q M Q L V Q S G A E V K K P G S S V K V S C K A S G G T F S S Y A I S W V R
Q A P G Q G L E W M G G I F G M F G T A N Y A Q K F Q G R V T I T A D E F T
S A A Y M E L S S L G S E D T A M Y Y C A R S S G Y Y P Q Y F Q D W G Q G T
L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y
F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T
V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T
C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V
V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R
V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A
K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I
A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S
R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:354

gaaattgtga tgacacagtc tccaggcacc ctgtctttgt ctccagggca aagagccacc 60
ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120
cctggccagg ctcccagact cctcatgtat ggtgcatcca gcagggccac tggcatccca 180
gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcatcgct cactttcggc 300
ggagggacca agctggagat caaacgtgcg gccgcaccca gcgtgttcat cttccccccc 360
tccgacgagc agctgaagag cggcaccgcc agcgtggtgt gcctgctgaa caacttctac 420
ccccgggagg ccaaggtgca gtggaaggtg gacaacgccc tgcagagcgg caacagccag 480
gagagcgtga ccgagcagga cagcaaggac tccacctaca gcctgagcag caccctcacc 540
ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaggtgac ccaccagggc 600
ctgagcagcc ccgtgaccaa gagcttcaac cggggcgagt gt 642

SEQ ID NO:355

E I V M T Q S P G T L S L S P G Q R A T L S C R A S Q S V S S S Y L A W Y Q
Q K P G Q A P R L L M Y G A S S R A T G I P D R F S G S G S G T D F T L T I
S R L E P E D F A V Y Y C Q Q Y G S S S L T F G G G T K L E I K R A A A P S
V F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q W K V D N
A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K
V Y A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:356

gaggtgcagc tggtggagtc cggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg catcttcaac agttatgcta tcagctgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggaggc atcatcgcta tctttcatac accaaagtac 180
gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgaa cacagcctac 240
atggaactga gaagcctgaa atctgaggac acggccctgt attactgtgc gagagggtcc 300
acttacgatt tttcgagtgg ccttgactac tggggccagg gaaccctggt caccgtctcg 360
agtgctagca ccaagggccc cagcgtgttc cccctggccc ccagcagcaa gagcaccagc 420
ggcggcacag ccgccctggg ctgcctggtg aaggactact tccccgagcc cgtgaccgtg 480
agctggaaca gcggcgcctt gaccagcggc gtgcacacct tccccgccgt gctgcagagc 540
agcggcctgt acagcctgag cagcgtggtg accgtgccca gcagcagcct gggcacccag 600
acctacatct gcaacgtgaa ccacaagccc agcaacacca aggtggacaa acgcgtggag 660
cccaagagct gcgacaagac ccacacctgc ccccccctgcc ctgcccccga gctgctgggc 720
ggaccctccg tgttcctgtt cccccccaag cccaaggaca ccctcatgat cagccggacc 780
cccgaggtga cctgcgtggt ggtggacgtg agccacgagg accccgaggt gaagttcaac 840
tggtacgtgg acggcgtgga ggtgcacaac gccaagacca agccccggga ggagcagtac 900
aacagcacct accgggtggt gagcgtgctc accgtgctgc accaggactg gctgaacggc 960
aaggagtaca agtgcaaggt gagcaacaag gccctgcctg cccccatcga gaagaccatc 1020
agcaaggcca agggccagcc ccgggagccc caggtgtaca ccctgccccc cagccgggag 1080
gagatgacca agaaccaggt gtccctcacc tgtctggtga agggcttcta ccccagcgac 1140
atcgccgtgg agtgggagag caacggccag cccgagaaca actacaagac cacccccct 1200
gtgctggaca gcgacggcag cttcttcctg tacagcaagc tcaccgtgga caagagccgg 1260
tggcagcagg gcaacgtgtt cagctgcagc gtgatgcacg aggccctgca caaccactac 1320
acccagaaga gcctgagcct gagccccggc aag 1353

SEQ ID NO:357

E V Q L V E S G A E V K K P G S S V K V S C K A S G G I F N S Y A I S W V R
Q A P G Q G L E W M G G I I A I F H T P K Y A Q K F Q G R V T I T A D E S T
N T A Y M E L R S L K S E D T A L Y Y C A R G S T Y D F S S G L D Y W G Q G
T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D
Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V
T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H
T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V
V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y
R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K
A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D
I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K
S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:358

caggcagggc tgactcagcc accctcggtg tcagtggccc caggacagac ggccaggatt 60
acctgtgggg gaaacaacat tggaagtaaa agtgtgcact ggtaccagca gaagccaggc 120
caggcccctg tcctagtcgt ctatgatgat agcgaccggc cctcagggat ccctgagcga 180
ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240
gatgaggccg actattactg tcaggtgtgg gatagtagta gtgatcatgt ggtattcggc 300
ggagggacca agctgaccgt cctaggtgcg gccgcaggcc agcccaaggc cgctcccagc 360
gtgaccctgt tccccccctc ctccgaggag ctgcaggcca acaaggccac cctggtgtgc 420
ctcatcagcg acttctaccc tggcgccgtg accgtggcct ggaaggccga cagcagcccc 480
gtgaaggccg gcgtggagac caccaccccc agcaagcaga gcaacaacaa gtacgccgcc 540
agcagctacc tgagcctcac ccccgagcag tggaagagcc accggagcta cagctgccag 600
gtgacccacg agggcagcac cgtggagaag accgtggccc ccaccgagtg cagc 654

SEQ ID NO:359

Q A G L T Q P P S V S V A P G Q T A R I T C G G N N I G S K S V H W Y Q Q K
P G Q A P V L V V Y D D S D R P S G I P E R F S G S N S G N T A T L T I S R
V E A G D E A D Y Y C Q V W D S S S D H V V F G G G T K L T V L G A A A G Q
P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V T V
A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P E Q
W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

SEQ ID NO:360

caggtccagc tggtgcagtc tggggctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagg cttcttcagc agctatgcta tcagctgggt gcgccaggcc 120
cctggacaag gacttgagtg gatgggggg gtcatcccta tctttcgtac agcaaactac 180
gcacagaact tccagggcag agtcaccatt accgcggacg aattcacatc gtatatggag 240
ctgagcagcc tgagatctga cgacacggcc gtgtattact gtgcgaggtt gaattaccat 300
gattcgggga cttattataa cgccccccgg ggctggttcg acccctgggg ccagggaacc 360
ctggtcaccg tctcgagtgc tagcaccaag ggccccagcg tgttccccct ggccccccagc 420
agcaagagca ccagcggcgg cacagccgcc ctgggctgcc tggtgaagga ctacttcccc 480
gagcccgtga ccgtgagctg gaacagcggc gccttgacca gcggcgtgca caccttcccc 540
gccgtgctgc agagcagcgg cctgtacagc ctgagcagcg tggtgaccgt gcccagcagc 600
agcctgggca cccagaccta catctgcaac gtgaaccaca agcccagcaa caccaaggtg 660
gacaaacgcg tggagcccaa gagctgcgac aagacccaca cctgcccccc ctgccctgcc 720
cccgagctgc tgggcggacc ctccgtgttc ctgttccccc ccaagcccaa ggacaccctc 780
atgatcagcc ggaccccccga ggtgacctgc gtggtggtgg acgtgagcca cgaggacccc 840
gaggtgaagt tcaactggta cgtggacggc gtggaggtgc acaacgccaa gaccaagccc 900
cgggaggagc agtacaacag cacctaccgg gtggtgagcg tgctcaccgt gctgcaccag 960
gactggctga acggcaagga gtacaagtgc aaggtgagca acaaggccct gcctgccccc 1020
atcgagaaga ccatcagcaa ggccaagggc cagccccggg agccccaggt gtacaccctg 1080
ccccccagcc gggaggagat gaccaagaac caggtgtccc tcacctgtct ggtgaagggc 1140
ttctacccca gcgacatcgc cgtggagtgg gagagcaacg gccagcccga gaacaactac 1200
aagaccaccc cccctgtgct ggacagcgac ggcagcttct tcctgtacag caagctcacc 1260
gtggacaaga gccggtggca gcagggcaac gtgttcagct gcagcgtgat gcacgaggcc 1320
ctgcacaacc actacaccca gaagagcctg agcctgagcc ccggcaag 1368

SEQ ID NO:361

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G G F F S S Y A I S W V R
Q A P G Q G L E W M G G V I P I F R T A N Y A Q N F Q G R V T I T A D E F T
S Y M E L S S L R S D D T A V Y Y C A R L N Y H D S G T Y Y N A P R G W F D
P W G Q G T L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G
C L V K D Y F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S
L S S V V T V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S
C D K T H T C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P
E V T C V V V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q
Y N S T Y R V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E
K T I S K A K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G
F Y P S D I A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K
L T V D K S R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:362

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atcaactgca agtccagcca gagtatttta aacagctcca acaataagaa ctacttagct 120
tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctacccgg 180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtagt 300
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agcggcaaca gccaggagag cgtgaccgag caggacagca aggactccac ctacagcctg 540
agcagcaccc tcaccctgag caaggccgac tacgagaagc acaaggtgta cgcctgcgag 600
gtgacccacc agggcctgag cagccccgtg accaagagct tcaaccgggg cgagtgt 657

SEQ ID NO:363

D I Q M T Q S P D S L A V S L G E K A T I N C K S S Q S I L N S S N N K N Y
L A W Y Q Q K P G Q P P K L L I Y W A S T R E S G V P D R F S G S G S G T D
F T L T I S S L Q A E D V A V Y Y C Q Q Y Y S S P P T F G Q G T K V E I K R
A A A P S V F I F P P S D E Q L K S G T A S V V C L L N N F Y P R E A K V Q

W K V D N A L Q S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D
Y E K H K V Y A C E V T H Q G L S S P V T K S F N R G E C

SEQ ID NO:364

caggtccagc tggtgcagtc tggagctgag gtgaagaagc ctgggtcctc ggtgaaggtc 60
tcctgcaagg cttctggagt caccttcagt tactatgcta tgagctgggt gcgacaggcc 120
cctggacaag ggcttgagtg gatgggagga atcagcccta tgtttgggac aacaacctac 180
gcacagaagt tccagggcag agtcacgatt actgcggacg actccacgag tacagcctac 240
atggaggtga ggagcctgag atctgaggac acggccgtgt attactgtgc gagatcttcg 300
aattactatg atagtgtata tgactactgg ggccagggaa ccctggtcac cgtctcgagt 360
gctagcacca agggccccag cgtgttcccc ctggccccca gcagcaagag caccagcggc 420
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tggaacagcg gcgccttgac cagcggcgtg cacaccttcc ccgccgtgct gcagagcagc 540
ggcctgtaca gcctgagcag cgtggtgacc gtgcccagca gcagcctggg cacccagacc 600
tacatctgca acgtgaacca caagcccagc aacaccaagg tggacaaacg cgtggagccc 660
aagagctgcg acaagaccca cacctgcccc ccctgccctg cccccgagct gctgggcgga 720
ccctccgtgt tcctgttccc ccccaagccc aaggacaccc tcatgatcag ccggacccct 780
gaggtgacct gcgtggtggt ggacgtgagc cacgaggacc ccgaggtgaa gttcaactgg 840
tacgtggacg gcgtggaggt gcacaacgcc aagaccaagc cccgggagga gcagtacaac 900
agcacctacc gggtggtgag cgtgctcacc gtgctgcacc aggactggct gaacggcaag 960
gagtacaagt gcaaggtgag caacaaggcc ctgcctgccc ccatcgagaa gaccatcagc 1020
aaggccaagg gccagccccg ggagccccag gtgtacaccc tgcccccag ccgggaggag 1080
atgaccaaga accaggtgtc cctcacctgt ctggtgaagg gcttctaccc cagcgacatc 1140
gccgtggagt gggagagcaa cggccagccc gagaacaact acaagaccac ccccctgtg 1200
ctggacagcg acggcagctt cttcctgtac agcaagctca ccgtggacaa gagccggtgg 1260
cagcagggca acgtgttcag ctgcagcgtg atgcacgagg ccctgcacaa ccactacacc 1320
cagaagagcc tgagcctgag ccccggcaag 1350

SEQ ID NO:365

Q V Q L V Q S G A E V K K P G S S V K V S C K A S G V T F S Y Y A M S W V R
Q A P G Q G L E W M G G I S P M F G T T T Y A Q K F Q G R V T I T A D D S T
S T A Y M E V R S L R S E D T A V Y Y C A R S S N Y Y D S V Y D Y W G Q G T
L V T V S S A S T K G P S V F P L A P S S K S T S G G T A A L G C L V K D Y
F P E P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T
V P S S S L G T Q T Y I C N V N H K P S N T K V D K R V E P K S C D K T H T
C P P C P A P E L L G G P S V F L F P P K P K D T L M I S R T P E V T C V V
V D V S H E D P E V K F N W Y V D G V E V H N A K T K P R E E Q Y N S T Y R
V V S V L T V L H Q D W L N G K E Y K C K V S N K A L P A P I E K T I S K A
K G Q P R E P Q V Y T L P P S R E E M T K N Q V S L T C L V K G F Y P S D I
A V E W E S N G Q P E N N Y K T T P P V L D S D G S F F L Y S K L T V D K S
R W Q Q G N V F S C S V M H E A L H N H Y T Q K S L S L S P G K

SEQ ID NO:366

cagtctgtcg tgacgcagcc gccctcggag tcagtggccc caggacagac ggccaggatt 60
acctgtgggg gacataacat tggaagtaat agtgtgcact ggtaccagca gaagccaggc 120
caggcccctg tgctggtcgt gtatgataat agcgaccggc cctcagggat ccctgagcga 180
ttctctggct ccaactctgg gaacacggcc accctgacca tcagcagggt cgaagccggg 240
gatgaggccg actattactg tcaggtgtgg ggtagtagta gtgaccatta tgtcttcgga 300
actgggacca aggtcaccgt cctaggtgcg gccgcaggcc agcccaaggc cgctcccagc 360
gtgaccctgt tccccccctc ctccgaggag ctgcaggcca acaaggccac cctggtgtgc 420
ctcatcagcg acttctaccc tggcgccgtg accgtggcct ggaaggccga cagcagcccc 480
gtgaaggccg gcgtggagac caccaccccc agcaagcaga gcaacaacaa gtacgccgcc 540
agcagctacc tgagcctcac ccccgagcag tggaagagcc accggagcta cagctgccag 600
gtgacccacg agggcagcac cgtggagaag accgtggccc ccaccgagtg cagc 654

SEQ ID NO:367

Q S V V T Q P P S E S V A P G Q T A R I T C G G H N I G S N S V H W Y Q Q K
P G Q A P V L V V Y D N S D R P S G I P E R F S G S N S G N T A T L T I S R
V E A G D E A D Y Y C Q V W G S S S D H Y V F G T G T K V T V L G A A A G Q
P K A A P S V T L F P P S S E E L Q A N K A T L V C L I S D F Y P G A V T V
A W K A D S S P V K A G V E T T T P S K Q S N N K Y A A S S Y L S L T P E Q
W K S H R S Y S C Q V T H E G S T V E K T V A P T E C S

Table 1: First round Vkappa, Vlambda and VH amplifications

Primer name	Primer nucleotide sequence	SEQ ID NO:
OK1 (HuVK1B)	GAC ATC CAG WTG ACC CAG TCT CC	144
OK2 (HuVK2)	GAT GTT GTG ATG ACT CAG TCT CC	145
OK3 (HuVK2B2)	GAT ATT GTG ATG ACC CAG ACT CC	146
OK4 (HuVK3B)	GAA ATT GTG WTG ACR CAG TCT CC	147
OK5 (HuVK5)	GAA ACG ACA CTC ACG CAG TCT CC	148
OK6 (HuVK6)	GAA ATT GTG CTG ACT CAG TCT CC	149
OCK (HuCK)	ACA CTC TCC CCT GTT GAA GCT CTT	150
OL1 (HuVL1A)*	CAG TCT GTG CTG ACT CAG CCA CC	151
OL1 (HuVL1B)*	CAG TCT GTG YTG ACG CAG CCG CC	152
OL1 (HuVL1C)*	CAG TCT GTC GTG ACG CAG CCG CC	153
OL2 (HuVL2B)	CAG TCT GCC CTG ACT CAG CC	154
OL3 (HuVL3A)	TCC TAT GWG CTG ACT CAG CCA CC	155
OL4 (HuVL3B)	TCT TCT GAG CTG ACT CAG GAC CC	156
OL5 (HuVL4B)	CAG CYT GTG CTG ACT CAA TC	157
OL6 (HuVL5)	CAG GCT GTG CTG ACT CAG CCG TC	158
OL7 (HuVL6)	AAT TTT ATG CTG ACT CAG CCC CA	159
OL8 (HuVL7/8)	CAG RCT GTG GTG ACY CAG GAG CC	160
OL9 (HuVL9)#	CWG CCT GTG CTG ACT CAG CCM CC	161
OL9 (HuVL10)#	CAG GCA GGG CTG ACT CAG	162
OCL (HuCL2)X	TGA ACA TTC TGT AGG GGC CAC TG	163
OCL (HuCL7)X	AGA GCA TTC TGC AGG GGC CAC TG	164
OH1(HuVH1B7A)+	CAG RTG CAG CTG GTG CAR TCT GG	165
OH1 (HuVH1C)+	SAG GTC CAG CTG GTR CAG TCT GG	166
OH2 (HuVH2B)	CAG RTC ACC TTG AAG GAG TCT GG	167
OH3 (HuVH3A)	GAG GTG CAG CTG GTG GAG	168
OH4 (HuVH3C)	GAG GTG CAG CTG GTG GAG WCY GG	169
OH5 (HuVH4B)	CAG GTG CAG CTA CAG CAG TGG GG	170
OH6 (HuVH4C)	CAG STG CAG CTG CAG GAG TCS GG	171
OH7 (HuVH6A)	CAG GTA CAG CTG CAG CAG TCA GG	172
OCM (HuCIgM)	TGG AAG AGG CAC GTT CTT TTC TTT	173

* Mix in 1:1:1 ratio
\# Mix in 1:1 ratio
X Mix in 1:1 ratio
\+ Mix in 1:1 ratio

Table 2: Second round Vkappa, Vlambda and VH amplifications

Primer name	Primer nucleotide sequence	SEQ ID NO
OK1S (HuVK1B-SAL)	TGA GCA CAC AGG TCG ACG GAC ATC CAG WTG ACC CAG TCT CC	174
OK2S (HuVK2-SAL)	TGA GCA CAC AGG TCG ACG GAT GTT GTG ATG ACT CAG TCT CC	175
OK3S (HuVK2B2-SAL)	TGA GCA CAC AGG TCG ACG GAT ATT GTG ATG ACC CAG ACT CC	176
OK4S (HuVK3B-SAL)	TGA GCA CAC AGG TCG ACG GAA ATT GTG WTG ACR CAG TCT CC	177
OK5S (HuVK5-SAL)	TGA GCA CAC AGG TCG ACG GAA ACG ACA CTC ACG CAG TCT CC	178
OK6S (HuVK6-SAL)	TGA GCA CAC AGG TCG ACG GAA ATT GTG CTG ACT CAG TCT CC	179
OJK1 (HuJK1-NOT)	GAG TCA TTC TCG ACT TGC GGC CGC ACG TTT GAT TTC CAC CTT GGT CCC	180
OJK2 (HuJK2-NOT)	GAG TCA TTC TCG ACT TGC GGC CGC ACG TTT GAT CTC CAG CTT GGT CCC	181
OJK3 (HuJK3-NOT)	GAG TCA TTC TCG ACT TGC GGC CGC ACG TTT GAT ATC CAC TTT GGT CCC	182
OJK4 (HuJK4-NOT)	GAG TCA TTC TCG ACT TGC GGC CGC ACG TTT GAT CTC CAC CTT GGT CCC	183
OJK5 (HuJK5-NOT)	GAG TCA TTC TCG ACT TGC GGC CGC ACG TTT AAT CTC CAG TCG TGT CCC	184
OL1S (HuVL1A-SAL)*	TGA GCA CAC AGG TCG ACG CAG TCT GTG CTG ACT CAG CCA CC	185
OL1S (HuVL1B-SAL)*	TGA GCA CAC AGG TCG ACG CAG TCT GTG YTG ACG CAG CCG CC	186
OL1S (HuVL1C-SAL)*	TGA GCA CAC AGG TCG ACG CAG TCT GTC GTG ACG CAG CCG CC	187
OL2S (HuVL2B-SAL)	TGA GCA CAC AGG TCG ACG CAG TCT GCC CTG ACT CAG CC	188
OL3S (HuVL3A-SAL)	TGA GCA CAC AGG TCG ACG TCC TAT GWG CTG ACT CAG CCA CC	189
OL4S (HuVL3B-SAL)	TGA GCA CAC AGG TCG ACG TCT TCT GAG CTG ACT CAG GAC CC	190
OL5S (HuVL4B-SAL)	TGA GCA CAC AGG TCG ACG CAG CYT GTG CTG ACT CAA TC	191
OL6S (HuVL5-SAL)	TGA GCA CAC AGG TCG ACG CAG GCT GTG CTG ACT CAG CCG TC	192
OL7S (HuVL6-SAL)	TGA GCA CAC AGG TCG ACG AAT TTT ATG CTG ACT CAG CCC CA	193
OL8S (HuVL7/8-SAL)	TGA GCA CAC AGG TCG ACG CAG RCT GTG GTG ACY CAG GAG CC	194
OL9S (HuVL9-SAL)#	TGA GCA CAC AGG TCG ACG CWG CCT GTG CTG ACT CAG CCM CC	195
OL9S (HuVL10-SAL)#	TGA GCA CAC AGG TCG ACG CAG GCA GGG CTG ACT CAG	196
OJL1 (HuJL1-NOT)	GAG TCA TTC TCG ACT TGC GGC CGC ACC TAG GAC GGT GAC CTT GGT CCC	197
OJL2 (HuJL2/3-NOT)	GAG TCA TTC TCG ACT TGC GGC CGC ACC TAG GAC GGT CAG CTT GGT CCC	198
OJL3 (HuJL7-NOT)	GAG TCA TTC TCG ACT TGC GGC CGC ACC GAG GAC GGT CAG CTG GGT GCC	199

OH1S (HuVH1B-SFI)+	GTC CTC GCA ACT GCG GCC CAG CCG GCC ATG GCC CAG RTG CAG CTG GTG CAR TCT GG	200
OH1S (HuVH1C-SFI)+	GTC CTC GCA ACT GCG GCC CAG CCG GCC ATG GCC SAG GTC CAG CTG GTR CAG TCT GG	201
OH2S (HuVH2B-SFI)	GTC CTC GCA ACT GCG GCC CAG CCG GCC ATG GCC CAG RTC ACC TTG AAG GAG TCT GG	202
OH3S (HuVH3A-SFI)	GTC CTC GCA ACT GCG GCC CAG CCG GCC ATG GCC GAG GTG CAG CTG GTG GAG	203
OH4S (HuVH3C-SFI)	GTC CTC GCA ACT GCG GCC CAG CCG GCC ATG GCC GAG GTG CAG CTG GTG GAG WCY GG	204
OH5S (HuVH4B-SFI)	GTC CTC GCA ACT GCG GCC CAG CCG GCC ATG GCC CAG GTG CAG CTA CAG CAG TGG GG	205
OH6S (HuVH4C-SFI)	GTC CTC GCA ACT GCG GCC CAG CCG GCC ATG GCC CAG STG CAG CTG CAG GAG TCS GG	206
OH7S (HuVH6A-SFI)	GTC CTC GCA ACT GCG GCC CAG CCG GCC ATG GCC CAG GTA CAG CTG CAG CAG TCA GG	207
OJH1 (HuJH1/2-XHO)	GAG TCA TTC TCG ACT CGA GAC RGT GAC CAG GGT GCC	208
OJH2 (HuJH3-XHO)	GAG TCA TTC TCG ACT CGA GAC GGT GAC CAT TGT CCC	209
OJH3 (HuJH4/5-XHO)	GAG TCA TTC TCG ACT CGA GAC GGT GAC CAG GGT TCC	210
OJH4 (HuJH6-XHO)	GAG TCA TTC TCG ACT CGA GAC GGT GAC CGT GGT CCC	211

* Mix in 1:1:1 ratio
\# Mix in 1:1 ratio
\+ Mix in 1:1 ratio

Table 3. Second round VL regions amplification overview

Template	5′ primer	3′ primer	Product	Share in PK/PL(%)	Pool	Share in VL (%)
K1	OK1S	OJK1	K1J1	25	PK1	30
	OK1S	OJK2	K1J2	25		
	OK1S	OJK3	K1J3	10		
	OK1S	OJK4	K1J4	25		
	OK1S	OJK5	K1J5	15		
K2	OK2S	OJK1	K2J1	25	PK2	4
	OK2S	OJK2	K2J2	25		
	OK2S	OJK3	K2J3	10		
	OK2S	OJK4	K2J4	25		
	OK2S	OJK5	K2J5	15		
K3	OK3S	OJK1	K3J1	25	PK3	1
	OK3S	OJK2	K3J2	25		
	OK3S	OJK3	K3J3	10		
	OK3S	OJK4	K3J4	25		
	OK3S	OJK5	K3J5	15		
K4	OK4S	OJK1	K4J1	25	PK4	19
	OK4S	OJK2	K4J2	25		
	OK4S	OJK3	K4J3	10		
	OK4S	OJK4	K4J4	25		
	OK4S	OJK5	K4J5	15		
K5	OK5S	OJK1	K5J1	25	PK5	1
	OK5S	OJK2	K5J2	25		
	OK5S	OJK3	K5J3	10		
	OK5S	OJK4	K5J4	25		
	OK5S	OJK5	K5J5	15		
K6	OK6S	OJK1	K6J1	25	PK6	5
	OK6S	OJK2	K6J2	25		
	OK6S	OJK3	K6J3	10		
	OK6S	OJK4	K6J4	25		
	OK6S	OJK5	K6J5	15		
L1	OL1S	OJL1	L1J1	30	PL1	14
	OL1S	OJL2	L1J2	60		
	OL1S	OJL3	L1J3	10		
L2	OL2S	OJL1	L2J1	30	PL2	10
	OL2S	OJL2	L2J2	60		
	OL2S	OJL3	L2J3	10		
L3	OL3S	OJL1	L3J1	30	PL3	10
	OL3S	OJL2	L3J2	60		
	OL3S	OJL3	L3J3	10		
L4	OL4S	OJL1	L4J1	30	PL4	1
	OL4S	OJL2	L4J2	60		
	OL4S	OJL3	L4J3	10		
L5	OL5S	OJL1	L5J1	30	PL5	1
	OL5S	OJL2	L5J2	60		
	OL5S	OJL3	L5J3	10		
L6	OL6S	OJL1	L6J1	30	PL6	1
	OL6S	OJL2	L6J2	60		
	OL6S	OJL3	L6J3	10		

L7	OL7S	OJL1	L7J1	30	PL7	1
	OL7S	OJL2	L7J2	60		
	OL7S	OJL3	L7J3	10		
L8	OL8S	OJL1	L8J1	30	PL8	1
	OL8S	OJL2	L8J2	60		
	OL8S	OJL3	L8J3	10		
L9	OL9S	OJL1	L9J1	30	PL9	1
	OL9S	OJL2	L9J2	60		
	OL9S	OJL3	L9J3	10		
					VL	100%

Table 4. Second round VH regions amplification overview

Template	5′ primer	3′ primer	Product	Share in PK/PL (%)	Pool	Share in VH (%)
H1	OH1S	OJH1	H1J1	10	PH1	25
	OH1S	OJH2	H1J2	10		
	OH1S	OJH3	H1J3	60		
	OH1S	OJH4	H1J4	20		
H2	OH2S	OJH1	H2J1	10	PH2	2
	OH2S	OJH2	H2J2	10		
	OH2S	OJH3	H2J3	60		
	OH2S	OJH4	H2J4	20		
H3	OH3S	OJH1	H3J1	10	PH3	25
	OH3S	OJH2	H3J2	10		
	OH3S	OJH3	H3J3	60		
	OH3S	OJH4	H3J4	20		
H4	OH4S	OJH1	H4J1	10	PH4	25
	OH4S	OJH2	H4J2	10		
	OH4S	OJH3	H4J3	60		
	OH4S	OJH4	H4J4	20		
H5	OH5S	OJH1	H5J1	10	PH5	2
	OH5S	OJH2	H5J2	10		
	OH5S	OJH3	H5J3	60		
	OH5S	OJH4	H5J4	20		
H6	OH6S	OJH1	H6J1	10	PH6	20
	OH6S	OJH2	H6J2	10		
	OH6S	OJH3	H6J3	60		
	OH6S	OJH4	H6J4	20		
H7	OH7S	OJH1	H7J1	10	PH7	1
	OH7S	OJH2	H7J2	10		
	OH7S	OJH3	H7J3	60		
	OH7S	OJH4	H7J4	20		
					VH	100%

Table 5: Characteristics of the individual IgM memory B cell libraries.

IgM memory libraries						
Donor	Cells		Libraries			
	Total PBL ($x10^6$)	% memory B cells	Size ($x10^6$)	% Insert frequency	% ORF	% Unique
Individual 1			3	96	74	98
Individual 2	72.5	1.7	5	98	79	98
Individual 3	67.5	1.4	3	96	79	98
Individual 4	132.5	2.3	6	98	69	99

Table 6: Data of the HA-specific single-chain Fvs.

Name scFv	SEQ ID NO (nucl sequence)	SEQ ID NO (amino acid sequence)*	VH-locus	VL-locus
SC06-141	212	213 (Vh 1-115; Vl 132-245)	VH1 (1-18)	VKIV (B3)
SC06-255	115	116 (Vh 1-121; Vl 138-248)	VH1 (1-69)	VL1 (V1-16)
SC06-257	117	118 (Vh 1-121; Vl 138-248)	VH1 (1-69)	VL2 (V1-4)
SC06-260	119	120 (Vh 1-121; Vl 138-248)	VH1 (1-69)	VL1 (V1-17)
SC06-261	121	122 (Vh 1-121; Vl 138-249)	VH1 (1-69)	VL1 (V1-19)
SC06-262	123	124 (Vh 1-120; Vl 137-245)	VH1 (1-69)	VKI (A20)
SC06-268	125	126 (Vh 1-120; Vl 137-243)	VH1 (1-69)	VL3 (V2-1)
SC06-272	214	215 (Vh 1-120; Vl 137-247)	VH1 (1-69)	VL2 (V1-3)
SC06-296	216	217 (Vh 1-121; Vl 138-246)	VH1 (1-2)	VKIII (A27)
SC06-301	218	219 (Vh 1-117; Vl 134-246)	VH1 (3-23)	VKII (A3)
SC06-307	127	128 (Vh 1-122; Vl 139-246)	VH3 (3-21)	VKIII (A27)
SC06-310	129	130 (Vh 1-121; Vl 138-246)	VH1 (1-69)	VL3 (V2-14)
SC06-314	131	132 (Vh 1-121; Vl 138-248)	VH1 (1-69)	VL1 (V1-17)
SC06-323	133	134 (Vh 1-120; Vl 137-245)	VH1 (1-69)	VKIII (A27)
SC06-325	135	136 (Vh 1-121; Vl 138-248)	VH1 (1-69)	VL2 (V1-4)
SC06-327	220	221 (Vh 1-121; Vl 138-246)	VH1 (1-69)	VL3 (V2-14)
SC06-328	222	223 (Vh 1-128; Vl 145-252)	VH1 (1-69)	VKIII (A27)

SC06-329	224	225 (Vh 1-121; Vl 138-246)	VH1 (1-69)	VKIII (A27)
SC06-331	137	138 (Vh 1-120; Vl 137-245)	VH1 (1-69)	VL3 (V2-14)
SC06-332	226	227 (Vh 1-120; Vl 137-243)	VH1 (1-69)	VKI (A20)
SC06-334	228	229 (Vh 1-120; Vl 137-245)	VH1 (1-69)	VL3 (V2-14)
SC06-336	230	231 (Vh 1-120; Vl 137-245)	VH1 (1-69)	VKIII (A27)
SC06-339	232	233 (Vh 1-121; Vl 138-246)	VH1 (1-69)	VL3 (V2-14)
SC06-342	234	235 (Vh 1-126; Vl 143-256)	VH1 (1-69)	VKIV (B3)
SC06-343	236	237 (Vh 1-120; Vl 137-245)	VH1 (1-69)	VL3 (V2-14)
SC06-344	139	140 (Vh 1-123; Vl 140-250)	VH1 (1-69)	VL1 (V1-13)

* between brackets the amino acids making up the heavy chain variable region (VH) and the light chain variable region (VL) is shown

Table 7: Data of the CDR regions of the *HA* specific immunoglobulins. The SEQ ID NO is given between brackets.

Name scFv	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
SC06-141	GYYVY (238)	WISAYNGNTNY AQKFQG (239)	SRSLDV (240)	KSSQSVLYSSN NKNYLA (241)	WASTRES (242)	QQYYSTPLT (243)
SC06-255	SYAIS (1)	GIIPIFGTTKY APKFQG (2)	HMGYQVRET MDV (3)	SGSTFNIGSNA VD (4)	SNNQRPS (5)	AAWDDILNV PV (6)
SC06-257	SYAIS (1)	GIIPIFGTTKY APKFQG (2)	HMGYQVRET MDV (3)	TGTSSDVGGYN YVS (7)	EVSNRPS (8)	SSYTSSSTY V (9)
SC06-260	SYAIS (1)	GIIPIFGTTKY APKFQG (2)	HMGYQVRET MDV (3)	SGSRSNVGDNS VY (10)	KNTQRPS (11)	VAWDDSVDG YV (12)
SC06-261	SYAIS (1)	GIIPIFGTTKY APKFQG (2)	HMGYQVRET MDV (3)	SGSSSNIGNDY VS (13)	DNNKRPS (14)	ATWDRRPTA YVV (15)
SC06-262	GSAIS (16)	GISPLFGTTNY AQKFQG (17)	GPKYYSEYM DV (18)	RASQGISSYLA (19)	DASTLRS (20)	QRYNSAPPI T (21)
SC06-268	SYAIS (1)	GIMGMFGTTNY AQKFQG (22)	SSGYYPEYF QD (23)	SGHKLGDKYVS (24)	QDNRRPS (25)	QAWDSSTAV (26)
SC06-272	SYAIT (244)	GIIGMFGSTNY AQNFQG (245)	STGYYPAYL HH (246)	TGTSSDVGGYN YVS (247)	DVSKRPS (248)	SSYTSSSTH V (249)
SC06-296	SYYMH (250)	WINPNSGGTNY AQKFQG (251)	EGKWGPQAA FDI (252)	RASQSVSSSYL A (253)	DASSRAT (254)	QQYGSSLW (255)
SC06-301	IYAMS (256)	AISSSGDSTYY ADSVKG (257)	AYGYTFDP (258)	RSSQSLLHSNG YNYLD (259)	LGSNRAS (260)	MQALQTPL (261)
SC06-307	SYSMN (27)	SISSSSSYIYY VDSVKG (28)	GGGSYGAYE GFDY (29)	RASQRVSSYLA (30)	GASTRAA (31)	QQYGRTPLT (32)
SC06-310	SYAIS (1)	GIIPIFGTTKY APKFQG (2)	HMGYQVRET MDV (3)	GGNNIGSKSVH (33)	DDSDRPS (34)	QVWDSSSDH AV (35)
SC06-314	SYAIS (1)	GIIPIFGTTKY APKFQG (2)	HMGYQVRET MDV (3)	SGSSSNIGSNY VY (36)	RDGQRPS (37)	ATWDDNLSG PV (38)
SC06-323	SYGIS (39)	DIIGMFGSTNY AQNFQG (40)	SSGYYPAYL PH (41)	RASQSVSSSYL A (42)	GASSRAT (43)	QQYGSSPRT (44)

SC06-325	FYSMS (45)	GIIPMFGTTNY AQKFQG (46)	GDKGIYYYY MDV (47)	TGTSSDVGGYN YVS (7)	EVSNRPS (8)	SSYTSSSTL V (48)
SC06-327	THAIS (262)	GIIAIFGTANY AQKFQG (263)	GSGYHISTP FDN (264)	GGNNIGSKGVH (265)	DDSDRPS (266)	QVWDSSSDH VV (267)
SC06-328	GYAIS (268)	GIIPIFGTTNY AQKFQG (269)	VKDGYCTLT SCPVGWYFD L (270)	RASQSVSSSYL A (271)	GASSRAT (272)	QQYGSSLT (273)
SC06-329	SNSIS (274)	GIFALFGTTDY AQKFQG (275)	GSGYTTRNY FDY (276)	RASQSVSSNYL G (277)	GASSRAS (278)	QQYGSSPLT (279)
SC06-331	SYAIS (1)	GIIGMFGTANY AQKFQG (49)	GNYYYESSL DY (50)	GGNNIGSKSVH (33)	DDSDRPS (34)	QVWDSSSDH YV (51)
SC06-332	NFAIN (280)	GIIAVFGTTKY AHKFQG (281)	GPHYYSSYM DV (282)	RASQGISTYLA (283)	AASTLQS (284)	QKYNSAPS (285)
SC06-334	SNAVS (286)	GILGVFGSPSY AQKFQG (287)	GPTYYYSYM DV (288)	GGNNIGRNSVH (289)	DDSDRPS (290)	QVWHSSSDH YV (291)
SC06-336	SYAIS (292)	GIFGMFGTANY AQKFQG (293)	SSGYYPQYF QD (294)	RASQSVSSSYL A (295)	GASSRAT (296)	QQYGSSSLT (297)
SC06-339	SYAIS (298)	GIIAIFHTPKY AQKFQG (299)	GSTYDFSSG LDY (300)	GGNNIGSKSVH (301)	DDSDRPS (302)	QVWDSSSDH VV (303)
SC06-342	SYAIS (304)	GVIPIFRTANY AQNFQG (305)	LNYHDSGTY YNAPRGWFD P (306)	KSSQSILNSSN NKNYLA (307)	WASTRES (308)	QQYYSSPPT (309)
SC06-343	YYAMS (310)	GISPMFGTTTY AQKFQG (311)	SSNYYDSVY DY (312)	GGHNIGSNSVH (313)	DNSDRPS (314)	QVWGSSSDH YV (315)
SC06-344	NYAMS (52)	GIIAIFGTPKY AQKFQG (53)	IPHYNFGSG SYFDY (54)	TGSSSNIGAGY DVH (55)	GNSNRPS (56)	GTWDSSLSA YV (57)

Table 8. Data of the HA-specific IgGs.

Name IgG	SEQ ID NO of nucl. sequence heavy chain	SEQ ID NO of amino acid sequence* heavy chain	SEQ ID NO of nucl. sequence light chain	SEQ ID NO of amino acid sequence* light chain
CR6141	316	317 (Vh 1-115)	318	319 (Vl 1-114)
CR6255	58	59 (Vh 1-121)	84	85 (Vl 1-111)
CR6257	60	61 (Vh 1-121)	86	87 (Vl 1-111)
CR6260	62	63 (Vh 1-121)	88	89 (Vl 1-111)
CR6261	64	65 (Vh 1-121)	90	91 (Vl 1-112)
CR6262	66	67 (Vh 1-120)	92	93 (Vl 1-109)
CR6268	68	69 (Vh 1-120)	94	95 (Vl 1-107)
CR6272	320	321 (Vh 1-120)	322	323 (Vl 1-111)
CR6296	324	325 (Vh 1-121)	326	327 (Vl 1-109)
CR6301	328	329 (Vh 1-117)	330	331 (Vl 1-113)
CR6307	70	71 (Vh 1-122)	96	97 (Vl 1-108)
CR6310	72	73 (Vh 1-121)	98	99 (Vl 1-109)
CR6314	74	75 (Vh 1-121)	100	101 (Vl 1-111)
CR6323	76	77 (Vh 1-120)	102	103 (Vl 1-109)
CR6325	78	79 (Vh 1-121)	104	105 (Vl 1-111)
CR6327	332	333 (Vh 1-121)	334	335 (Vl 1-109)
CR6328	336	337 (Vh 1-128)	338	339 (Vl 1-108)
CR6329	340	341 (Vh 1-121)	342	343 (Vl 1-109)
CR6331	80	81 (Vh 1-120)	106	107 (Vl 1-109)
CR6332	344	345 (Vh 1-120)	346	347 (Vl 1-107)
CR6334	348	349 (Vh 1-120)	350	351 (Vl 1-109)
CR6336	352	353 (Vh 1-120)	354	355 (Vl 1-109)
CR6339	356	357 (Vh 1-121)	358	359 (Vl 1-109)
CR6342	360	361 (Vh 1-126)	362	363 (Vl 1-114)

CR6343	364	365 (Vh 1-120)	366	367 (Vl 1-109)
CR6344	82	83 (Vh 1-123)	108	109 (Vl 1-111)

* between brackets the amino acids making up the heavy chain variable region (VH) and the light chain variable region (VL) is shown

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Table 9. Binding of IgGs to HA (H5N1TV)-expressing PER.C6 cells.

	HA (H5N1TV)-expressing PER.C6 cells			Control PER.C6 cells		
Antibody	10 µg/ml	1 µg/ml	0.1 µg/ml	10 µg/ml	1 µg/ml	0.1 µg/ml
CR6255	414.18	257.13	60.43	3.16	2.64	2.48
CR6257	365.17	283.87	62.08	2.59	2.44	2.53
CR6260	323.42	168.49	31.06	5.42	3.34	2.57
CR6261	330.77	278.81	85.82	29.43	13.22	3.89
CR6262	84.29	20.91	8.06	2.71	2.53	2.48
CR6268	421.70	218.70	43.71	3.82	2.74	2.50
CR6307	484.78	266.55	82.42	4.87	3.02	2.48
CR6314	399.54	166.98	44.51	5.99	3.49	2.64
CR6323	445.08	116.52	33.38	5.05	2.92	2.71
CR6325	478.29	239.28	64.36	4.00	3.11	2.57
CR6344	768.25	328.16	106.65	80.90	26.33	10.17
CR3014	13.10	10.00	6.21	3.11	2.69	2.55
CR6310*	597.04	290.93	86.91	14.92	6.05	4.42
CR6331*	421.14	165.43	41.04	7.87	4.59	4.55
CR3014*	9.15	7.95	10.51	4.74	4.12	4.57

* Indicates FACS analyses that were performed in a separate experiment

Table 10. Potency of the anti-HA antibodies in the neutralizing antibody titer assay.

Antibody	Concentration (µg/ml)
CR6255	25
CR6257	12.5
CR6260	12.5
CR6261	12.5
CR6262	100
CR6268	50
CR6307	50
CR6314	12.5
CR6323	50
CR6325	12.5
CR6344	25
CR6310	25
CR6331	100
CR4098	-*

*At 50 µg/ml no neutralization was observed

Table 11. Potency of the anti-HA antibodies in the neutralizing antibody titer assay.

Antibody	Concentration (µg/ml)
CR6255	3.12
CR6257	1.56
CR6260	3.12
CR6261	0.78
CR6262	25
CR6268	6.25
CR6272	-
CR6307	25
CR6310	6.25
CR6314	3.12
CR6323	6.25
CR6325	6.25
CR6327	6.25
CR6328	25
CR6329	3.12
CR6331	25
CR6332	12.5
CR6334	6.25
CR6336	25
CR6339	-
CR6342	6.25
CR6343	50
CR6344	25

- means at 100 µg/ml no neutralization was observed

Table 12. Cross-reactivity of anti-H5N1 IgGs to HA molecules of different HA subtypes as measured by ELISA (OD 492nm). ND: Not determined

	H1	H3	H5	H7	H9	BPL-inact. A/NC/20/99 (H1N1)	BPL-inact. NIBRG14 (H5N1)
CR6255	1.91	0.08	1.44	0.22	1.97	1.38	1.18
CR6257	1.93	0.08	1.37	0.16	2.06	1.34	1.21
CR6260	1.88	0.08	1.45	0.19	2.00	1.34	1.17
CR6261	2.04	0.07	1.44	0.31	2.32	1.46	1.41
CR6262	1.48	0.09	1.02	0.17	1.93	0.51	0.35
CR6268	1.78	0.08	1.30	0.15	2.16	1.39	1.13
CR6272	0.81	0.07	0.58	0.15	0.96	0.92	0.79
CR6307	0.22	0.11	0.99	0.22	0.17	0.23	0.50
CR6310	1.92	0.08	1.37	0.18	2.17	1.31	1.00
CR6314	1.93	0.07	1.48	0.25	2.21	1.37	1.42
CR6323	2.32	0.07	1.89	0.15	2.27	1.40	0.93
CR6325	1.42	0.07	1.30	0.17	2.04	1.09	1.20
CR6327	1.75	0.08	1.11	0.14	1.93	1.16	0.73
CR6328	2.43	0.07	1.78	0.16	2.38	1.39	0.98
CR6329	1.98	0.08	1.43	0.17	2.16	1.04	1.01
CR6331	1.75	0.06	1.32	0.16	2.02	1.25	0.92
CR6332	2.20	0.15	1.65	0.26	2.11	1.20	1.11
CR6334	2.04	0.07	1.19	0.15	1.82	1.13	0.91
CR6336	1.92	0.10	1.41	0.18	2.02	1.09	0.94
CR6339	1.25	0.07	0.81	0.14	1.96	0.94	0.50
CR6342	1.99	0.09	1.25	0.17	2.13	1.32	0.90
CR6343	1.28	0.07	0.76	0.15	1.88	0.91	0.64
CR6344	1.80	0.09	1.31	0.18	2.15	1.31	0.96
CR5111	0.08	0.07	1.57	0.15	0.17	0.09	0.81
CR3014	0.08	0.07	0.09	0.17	0.16	0.09	0.11
No IgG	0.13	0.08	0.09	0.15	0.16	0.09	0.14
Sheep anti-H5	ND	ND	ND	0.90	2.07	2.62	2.93

Table 13. Epitope mapping of human anti-HA antibodies.

	HA1	HA2	CR5111	CR6342 C179	CR6307 CR6323	CR6261 CR6325 CR6329
H5N1TV	TGLRN	GVTNKVNSIIDK	+	+	+	+
Mutant I	K----	----------	+	-	+	+
Mutant II	-----	-----E------	+	-	+	-
Mutant III	--M--	----------	+	+	+	+
Mutant IV	-----	-------R----	+	-	+	+
Mutant V	-----	----------N-	+	+	+	+

Table 14. Clinical scores of mice pre-treated with antibody, followed by a lethal challenge with H5N1 influenza virus

		Number of mice showing clinical signs[a]																						
		Study day																						
Group ID	Ab-dose (mg/kg)	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	CR6261-15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9
2	CR6261-5	0	0	0	0	0	0	0	0	0	0	0	2/9	2/9	1/8	0/7	0/7	0/7	0/7	0/7	0/7	0/7	0/7	0/7
3	CR6261-2	0	0	0	0	0	0	0	2	5	5	4/9	3/8	0/7	0/7	0/7	0/7	0/7	0/7	0/7	0/7	0/7	0/7	0/7
4	CR6261-0.7	0	0	0	0	0	0	10	10	8/8	7/7	7/7	6/6	4/4	4/4	4/4	4/4	4/4	4/4	4/4	1/4	1/4	1/4	1/4
5	CR6323-15	0	0	0	0	0	0	1	1	1	1	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9
6	CR6325-15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	RaH5N3	0	0	0	0	0	0	5	10	10	6/6	1/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
8	CR3014-15	0	0	0	0	10	10	10	10	9/9	5/5	1/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

[a]out of 10 unless indicated otherwise

Table 15. Respiratory distress of mice pre-treated with antibody, followed by a lethal challenge with H5N1 influenza virus

		Number of mice showing respiratory distress[a]																						
		Study day																						
Group ID	Ab-dose (mg/kg)	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	CR6261-15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	CR6261-5	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0	0	0	0	0	0
3	CR6261-2	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
4	CR6261-0.7	0	0	0	0	0	0	0	0	8	7	7	6	4	4	4	4	4	4	0	0	0	0	0
5	CR6323-15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	CR6325-15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	RaH5N3	0	0	0	0	0	0	0	0	10	6	1	1	-	-	-	-	-	-	-	-	-	-	-
8	CR3014-15	0	0	0	0	0	0	0	10	9	5	1	1	-	-	-	-	-	-	-	-	-	-	-

Table 16. Clinical scores of mice infected with H5N1 virus and treated with antibody at different time points post-infection

		Number of mice showing clinical signs[a]																					
		Study day																					
Group ID	Time interval p.i.	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	4 h	0	0	0	4	4	2	2	2	0	0	0	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9	0/9
2	1 d	0	0	0	10	10	10	10	10	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	2 d	0	0	0	3	10	10	10	10	8	9	9	8	5	4	2	0	0	0	0	0	0	0	0
4	3 d	0	0	0	5	5	10	10	10	10	10	10	10	10	3	3	2	0	0	0	0	0	0	0
5	CR2006	0	0	0	3	7	10	10	10	8/6	1/1	0	0	0	0	0	0	0	0	0	0	0	0	0

[a] with 14 mice in groups 2 and 5 until day 6 p.i.

Table 17. Respiratory distress of mice infected with H5N1 virus and treated with antibody at different time points post-infection

		Number of mice showing respiratory distress[a]																					
		Study day																					
Group ID	Time interval p.i.	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	4 h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1 d	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	2 d	0	0	0	0	0	0	10	10	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	3 d	0	0	0	0	0	0	10	10	5	9	7	7	4	1	0	0	0	0	0	0	0	0	0
5	CR2006	0	0	0	0	0	0	10	10	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0

[a] score 3

Table 18. Mortality of mice infected with H5N1 virus and treated with antibody at different time points post-infection

		Number of living mice on each study day																					
		Study day																					
Group ID	Time interval p.i.	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	4 h	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9	9	9	9	9	9	9
2	1 d	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
3	2 d	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4	3 d	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
5	CR2006	10	10	10	10	10	10	10	10	6	1	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 19. Mortality of mice infected with H1N1 virus and treated with antibody at different time points prior- and post-infection

	Number of living mice on each study day																					
	Study day																					
Time interval p.i.	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
-1d	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1d	10	10	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
2d	10	10	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8
3d	10	10	10	10	10	10	10	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8
control	10	10	10	10	10	10	10	10	5	2	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 20. Clinical scores of mice infected with H1N1 virus and treated with antibody at different time points prior- and post-infection

		Number of mice showing clinical signs[a]																					
		Study day																					
Group ID	Time interval p.i.	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
6	d -1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	d1	0	0	0	9	9	9	9	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	d2	0	0	0	9	9	9	9	9	9	8/8	8/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8
8	d3	0	0	0	10	10	10	10	9/9	9/9	8/8	8/8	8/8	8/8	8/8	4/8	3/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8
7	control	0	0	0	10	10	10	10	10	5/5	2/2													

[a] with 9 mice in the 1d and 2d p.i. treatment groups

Table 21. Respiratory distress of mice infected with H1N1 virus and treated with antibody at different time points prior- and post-infection

	Number of mice showing respiratory distress[a]																					
	Study day																					
Time interval p.i.	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1d	0	0	0	4	7	10	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2d	0	0	0	7	8	10	9	3	4	2	0	0	0	0	0	0	0	0	0	0	0	0	0
3d	0	0	0	4	10	9	10	9	9	8	8	8	8	6	0	0	0	0	0	0	0	0	0
ctrl	0	0	0	1	9	7	10	10	5	2													

[a] a score of 2 or 3

Table 22. Sequence of HA2 epitope in different influenza subtypes. The underlined amino acid represents the valine (V) -> glutamic acid (E) substitution in the H2N2 escape mutant (mutant II; Table 13)

	HA2	SEQ ID NO:
H5N1: A/Vietnam/1203/2004	GVTNKVNSIIDK	368
H5N1: A/Hong Kong/156/97	GVTNKVNSIINK	369
H5N2: A/mald/PA/84	GVTNKVNSIIDK	368
H1N1: A/PR/8/34 A/South Carolina/1/1918 A/WSN/33 A/New Caledonia/20/99 A/Bangkok/10/83 A/Yamagata/120/86	GITNKVNSVIEK	372
H2N2: A/Okuda/57 A/Kumamoto/1/65 A/Korea/426/68 A/Izumi/5/65	GITNKVNSVIEK	372
H2N2: A/Izumi/5/65 (R)	GITNKENSVIEK	373
H6N2: A/Mallard/Netherlands/16/99	GITNKVNSIIDK	374
H9N2: A/Hong Kong/1073/99	KITSKVNNIVDK	375
H3N2: A/Aichi/2/68	QINGKLNRVIEK	376
H3N2: A/Fukuoka/C29/85	QINGKLNRLIEK	377

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CLAIMS

1. An isolated human antibody capable of recognizing and binding to an epitope in the HA2 subunit of the influenza haemagglutinin protein (HA), characterized in that said binding molecule has neutralizing activity against an influenza virus comprising HA of the H5 subtype and wherein said antibody also has neutralizing activity against an influenza virus comprising HA of the H1 subtype, wherein the antibody comprises a heavy chain CDR1 region of SEQ ID NO:1, a heavy chain CDR2 region of SEQ ID NO:2, a heavy chain CDR3 region of SEQ ID NO:3, a light chain CDR1 region of SEQ ID NO:13, a light chain CDR2 region of SEQ ID NO:14, and a light chain CDR3 region of SEQ ID NO:15.

2. An antibody according to claim 1, wherein the antibody comprises a heavy chain variable region comprising the amino acids 1-121 of SEQ ID NO: 65, and a light chain variable region comprising the amino acids 1-112 of SEQ ID NO: 91.

3. A nucleic acid molecule encoding an antibody according to claim 1 or 2.

4. An antibody according to claim 1 or 2 for use as a medicament and preferably for the diagnostic, therapeutic and/or prophylactic treatment of influenza infection.

5. An antibody according to claim 4, wherein said influenza infection is caused by an influenza virus that is associated with a pandemic outbreak, or has the potential to be associated with a pandemic outbreak.

6. An antibody according to claim 5, wherein said influenza virus strain that is associated with a pandemic outbreak is selected from the group consisting of: H1N1, H5N1, H5N2, H5N8, H5N9, an H2-based strain, and H9N2.

7. A pharmaceutical composition comprising an antibody according to any of the claims 1-6, and a pharmaceutically acceptable excipient.

8. Use of an antibody according to any of the claims 1-6 in the preparation of a medicament for the diagnosis, prophylaxis, and/or treatment of an influenza virus infection.