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(54) **Title:** ISOLATION OF ANTI-DESMOGLEIN 1 ANTIBODIES BY PHAGE DISPLAY OF PEMPHIGUS FOLIACEUS AUTOANTIBODIES

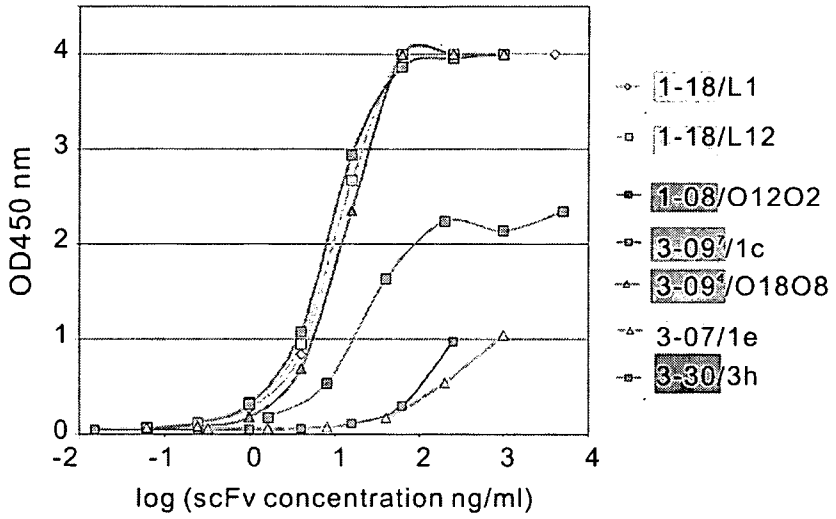

FIGURE 1

(57) **Abstract:** This invention relates to compositions and methods for the use of anti- autoimmune reagents that specifically bind to anti-desmoglein antibodies, which are responsible for pemphigus foliaceus. In addition, the invention relates to methods and compositions for inhibiting the expression or function of a variable region of an anti- desmoglein (anti-Dsg) pathogenic autoantibody.

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TITLE OF THE INVENTION

Isolation of Anti-Desmoglein 1 Antibodies by Phage Display of Pemphigus Foliaceus Autoantibodies

BACKGROUND OF THE INVENTION

Pemphigus foliaceus (PF) is a tissue-specific autoimmune disease in which antibodies against the keratinocyte cell surface cause skin blisters. These blisters are due to loss of cell adhesion in the superficial living epidermis (i.e. the granular layer) as shown by the diagnostic histology from biopsies of the skin lesions of these patients. The autoantibodies bind desmoglein 1 (Dsg1), a desmosomal cadherin found predominantly in the superficial layers of stratified squamous epithelia. Desmogleins are thought to function as cell-cell adhesion molecules which, in epidermis, maintain its integrity. Polyclonal anti-Dsg1 antibodies from PF patients are pathogenic in organ culture of normal human skin and by passive transfer to neonatal mice, which result in blisters with the typical histology of PF from loss of cell-cell adhesion.

In most PF patients the predominant antibody response is directed against the amino terminal 161 amino acids of the 496 amino acids in the extracellular domain of Dsg1. These antibodies directed against the amino terminus, where the trans-adhesion binding site is located, are necessary for pathogenicity. Furthermore, in the preclinical phase of fogo selvagem, a form of endemic PF in Brazil, patients develop IgG1 antibodies against the carboxy-terminus of the extracellular domain of Dsg1. In clinically affected patients, the antibody response migrates to an IgG4 antibody against the amino-terminus of Dsg1. The switch from an IgG1 to an IgG4 response is believed to indicate a maturation of the immune response. This switch does not implicate the Fc region of IgG as necessary for disease because neither the effector region of IgG nor crosslinking by IgG is necessary for these PF antibodies to cause blisters.

Study of PF serum-derived polyclonal antibodies has limitations for addressing many of the remaining questions regarding the pathophysiology of the autoantibodies in this disease. For example, it has yet to be determined whether antibodies directed against the amino-terminus of Dsg1 are both necessary and sufficient for disease. In order to consider the feasibility of developing specific therapy targeted to pathogenic autoantibodies, it is necessary to determine the genetic diversity of PF antibodies and whether specific antibody genes are preferentially used to produce them. Therefore, there

has been a long felt need in the field for more specific antibody-targeted therapies for pemphigus that would suppress or eliminate only the anti-Dsg autoantibodies. The present invention satisfies this need.

SUMMARY OF THE INVENTION

The present invention includes an isolated anti-desmoglein 1 (Dsg1) antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

In one embodiment, the antibody or fragment thereof of is pathogenic and comprises a consensus sequence represented by Asp-X-X-X-Trp (SEQ ID NO: 259) or Glu-X-X-X-Trp (SEQ ID NO: 260).

In another embodiment, the antibody or fragment thereof of comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof. In another embodiment, the antibody or fragment thereof of comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof. In yet another embodiment, the antibody or fragment thereof of comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 44-86, and any combination thereof.

In one embodiment, antibody or fragment thereof is a single chain Fv (scFv), a Fab, a $(Fab')_2$ or a $(scFv')_2$.

The present invention also includes a composition comprising an anti-autoimmune reagent, wherein the anti-autoimmune reagent specifically binds to an anti-desmoglein 1 (Dsg1) antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

In one embodiment, the anti-autoimmune reagent is selected from the group consisting of a peptide, a small molecule, an antibody, a humanized antibody, a recombinant antibody, and any combination thereof.

In another embodiment, the anti autoimmune reagent specifically binds to antibody or fragment thereof of comprising a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

In another embodiment, the anti autoimmune reagent specifically binds to antibody or fragment thereof of comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

In another embodiment, the anti autoimmune reagent specifically binds to antibody or fragment thereof comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 44-86, and any combination thereof.

The invention also includes an isolated nucleic acid sequence having at least 85% complementarity to a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

The invention also includes an inhibitor of an anti-desmoglein autoantibody or fragment thereof, wherein the inhibitor inhibits the expression of a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

In one embodiment, the inhibitor is selected from the group consisting of a small interfering RNA (siRNA), a microRNA, an antisense nucleic acid, a ribozyme, a polyamide, a triple-helix-forming agent, a synthetic peptide nucleic acids (PNAs), an agRNA, a LNA/DNA copolymer, and any combination thereof.

The invention also provides a method of inhibiting the binding of an anti-desmoglein 1 autoantibody or fragment thereof to desmoglein. The method comprises contacting the anti-desmoglein 1 autoantibody or fragment thereof with a composition comprising an anti-autoimmune reagent that specifically binds to an anti-desmoglein 1 autoantibody or fragment thereof. Preferably, the antibody or fragment thereof is associated with the pathology of pemphigus foliaceus (PF)

In one embodiment, the anti-desmoglein 1 antibody or fragment thereof comprises a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

In another embodiment, the antibody or fragment thereof of comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

In yet another embodiment, the antibody or fragment thereof of comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

In another embodiment, the antibody or fragment thereof of comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 44-86, and any combination thereof.

The invention provides a method of modulating the expression of an anti-desmoglein autoantibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof. The method comprises contacting a nucleotide sequence encoding an anti-desmoglein autoantibody or fragment thereof with an inhibitor of an anti-desmoglein autoantibody or fragment thereof, wherein the inhibitor is inhibits the expression of said anti-desmoglein autoantibody or fragment thereof.

In one embodiment, the nucleotide sequence encoding an anti-desmoglein autoantibody or fragment thereof is a sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

In another embodiment, the nucleotide sequence encoding an anti-desmoglein autoantibody or fragment thereof is at least 85% homology to a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

The invention provides a method of treating an autoimmune pathology associated with pemphigus foliaceus (PF). The method comprises administering to a subject in need thereof a composition comprising an anti-autoimmune reagent that specifically binds to an anti-desmoglein 1 autoantibody or fragment thereof, thereby inhibiting the binding of the anti-desmoglein 1 autoantibody or fragment thereof to desmoglein.

In one embodiment, the anti-desmoglein 1 antibody or fragment thereof comprises a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

In another embodiment, the anti-autoimmune reagent is selected from the group consisting of a peptide, a small molecule, an antibody, a humanized antibody, a recombinant antibody, and any combination thereof.

In another embodiment, the antibody or fragment thereof of comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

In yet another embodiment, the antibody or fragment thereof of comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

In still yet another embodiment, the antibody or fragment thereof of comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 1-43, and any combination thereof.

The invention includes a method of treating an autoimmune pathology associated with pemphigus foliaceus (PF). The method comprising contacting a nucleotide sequence of the subject encoding an anti-desmoglein 1 antibody or fragment thereof with an inhibitor capable of inhibiting the expression of the nucleotide sequence encoding the anti-desmoglein autoantibody or fragment thereof, thereby inhibiting the expression of the anti-desmoglein autoantibody or fragment thereof.

In one embodiment, the anti-desmoglein 1 antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof

In another embodiment, the nucleotide sequence encoding an anti-desmoglein 1 autoantibody or fragment thereof is a sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

In another embodiment, the nucleotide sequence encoding an anti-desmoglein autoantibody or fragment thereof is at least 85% homology to a sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

In yet another embodiment, the inhibitor is selected from the group consisting of a small interfering RNA (siRNA), a microRNA, an antisense nucleic acid, a ribozyme, a polyamide, a triple-helix-forming agent, a synthetic peptide nucleic acids (PNAs), an agRNA, a LNA/DNA copolymer, and any combination thereof.

The invention includes a method of depleting a biological sample from an anti-desmoglein 1 antibody or fragment thereof. The method comprises contacting the sample with an immobile composition comprising an anti-autoimmune reagent capable of specifically binding to an anti-desmoglein 1 autoantibody or fragment thereof; and removing the biological sample without the bound anti-desmoglein 1 autoantibody or fragment thereof, thereby depleting the biological sample of anti-desmoglein 1 autoantibody or fragment thereof.

In one embodiment, the anti-desmoglein 1 antibody or fragment thereof comprises a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof

In another embodiment, the anti-desmoglein autoantibody or fragment thereof is associated with the pathology of pemphigus foliaceus (PF).

In another embodiment, the anti-desmoglein 1 autoantibody or fragment thereof comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

In another embodiment, the anti-desmoglein 1 autoantibody or fragment thereof comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

In yet another embodiment, the anti-desmoglein 1 autoantibody or fragment thereof comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 1-43, and any combination thereof.

In another embodiment, the step of contacting the sample with an immobile composition is carried out during a plasmapheresis procedure performed on a subject.

The invention provides a method of diagnosing pemphigus foliaceus (PF) in a subject. The method comprising contacting a biological sample of a subject with a composition comprising an anti-autoimmune reagent that specifically binds to an anti-desmoglein 1 autoantibody or fragment thereof; and analyzing the biological sample for the presence of antibody-antigen complex, whereby the presence of antibody-antigen complex indicates the subject has or is predisposed to pemphigus foliaceus (PF).

In one embodiment, the anti-autoimmune reagent specifically binds to an anti-desmoglein 1 (Dsg1) antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

In another embodiment, the anti-autoimmune reagent is selected from the group consisting of a peptide, a small molecule, an antibody, a humanized antibody, a recombinant antibody, and any combination thereof.

In another embodiment, the antibody or fragment thereof of comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

In yet another embodiment, the antibody or fragment thereof of comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

In another embodiment, the antibody or fragment thereof of comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 1-43, and any combination thereof.

In one embodiment, contacting the biological sample with the composition comprising an anti-autoimmune reagent is evaluated using a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, or a combination thereof.

Other features and advantages of the present invention will become apparent from the following detailed description examples and figures. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

For the purpose of illustrating the invention, there are depicted in the drawings certain embodiments of the invention. However, the invention is not limited to the precise arrangements and instrumentalities of the embodiments depicted in the drawings.

Figure 1 is a graph depicting serial dilutions of representative scFvs that were measured by Dsg1 ELISA. Clones 1-18/L1 and 1-18/L12 (light green lines) and 3-094/O18O8 and 3-097/1c (dark green lines) are depicted. Clones 1-08/O12O2 and 3-07/1e showed weak binding to Dsg1 as measured by ELISA. Clone 3-30/3h exhibited intermediate binding capacity.

Figure 2, comprising Figures 2A-2C, is a series of impages depicting an indirect immunofluorescence micrograph of anti-Dsg1 scFvs on human skin. Clone 3-30/3h scFv antibodies stained the cell surface of keratinocytes throughout human epidermis (Figure 2A). Pretreatment of human skin with EDTA prevented cell suface staining by 3-30/3h (Figure 2B). Clone 3-094/O18O8 showed cytoplasmic staining in the superficial layers of the epidermis (Figure 2C).

Figure 3, comprising Figures 3A and 3B, is a series of images depicting the purified ectodomain of human Dsg1 with an E-tag (Dsg1-EHis), produced by baculovirus

that was used as an immunoblot substrate. ScFv heavy chain variable regions encoded by the gene VH1-18, but not other scFvs, bound denatured Dsg1 on immunoblots (Figure 3A). Figure 3B represents a gel showing recombinant human Dsg1 or Dsg4 containing an E-tag (Dsg1-EHis or Dsg4-EHis), produced by baculovirus, immunoprecipitated with representative anti-Dsg1 scFvs, control scFv (AM3-13), or Talon metal affinity resin (Ni-beads) and detected on an immunoblot by anti-E tag antibody.

Figure 4 is a chart depicting an epitope mapping. Wild-type and domain-swapped extracellular domains of human Dsg1 and Dsg3 were produced by baculovirus and used as competitors in ELISA. The molecular structure of domain-swapped molecules is shown. "+" indicates greater than 40% inhibition.

Figure 5, comprising Figures 5A and 5B, is a series of images demonstrating that a monovalent monoclonal anti-Dsg1 scFv causes typical PF blister formation in neonatal mice and human skin. Figure 5A shows passive transfer of anti-Dsg1 scFvs into neonatal mice. Images were taken 6 hours after subcutaneous injection of scFvs. The gross appearance of the mice, and their skin histology and direct immunofluorescence are shown. Injection of 3-30/3h scFv caused gross blisters on the back (arrow) due to blistering in the granular layer of the epidermis. Direct immunofluorescence showed binding of these scFvs to the cell surface of the mouse epidermis. Figure 5B depicts the pathogenicity assay using human skin. Anti-Dsg1 scFvs were injected into human skin specimens which were then cultured for 24 hours. Histology and direct immunofluorescence of the skin are shown. All scFvs, except 3-94/O18O8, bound the cell surface of epidermal keratinocytes. 3-7/1e and 3-30/3h caused PF-like superficial epidermal blisters.

Figure 6, comprising Figures 6A and 6B demonstrates that multiple pemphigus sera target the same or nearby epitopes defined by anti-Dsg1 scFvs. Figure 6A shows six PF sera, 5 mucocutaneous PV sera which contain Dsg1 and Dsg3 antibodies (PV(3+1)), 3 mucosal PV sera containing only Dsg3 antibody (PV (3)) and a normal control serum (N), were used to block the binding of pathogenic scFv clone 3-30/3h to Dsg1. All PF sera and all PV(3+1) sera tested inhibit the binding of 3-30/3h. Figure 6B shows the binding of PF sera to Dsg1 was blocked by poly scFvs P3 (a mixture of scFvs derived from clones that bind Dsg1 after three rounds of routine pannings, and which contain almost all non-pathogenic scFvs as shown from previous characterization of these clones), pathogenic scFvs (3-07/1e and 3-30/3h) or a combination of poly scFvs P3 and pathogenic scFvs. Serum from PF patient 1 from which the phage library was made (PF1-lib) and four other PF sera were tested. These results show that the scFv isolated by phage display from PF patient

1 block most epitopes bound by other PF sera, and that other PF sera bind the epitopes (or nearby epitopes) defined by the two pathogenic clones.

Figure 7, comprising Figures 7A through 7C, is a series of charts depicting ScFv used for ELISA on Dsg1 and Dsg3. Phage panned on Dsg3 (or its scFv) showed positive Dsg3 binding on ELISA. One phage clone, D(3)4-3 showed slight binding to Dsg1 (Figures 7A and 7B). Phage or scFv derived from Dsg3/Dsg1 alternating panning scheme showed binding to both desmogleins by ELISA (Figure 7C).

Figure 8, comprising Figures 8A and 8B, shows inhibition of H44L4 (an anti-α2bβ3 platelet monoclonal autoantibody) to α2bβ3 by the respective peptides. Figure 8A depicts a bar graph showing that peptides P4-12 and P4-7 (from a linear 12-mer library) and P4-2a and P3-4 (from a constrained 7-mer "C7C" library) inhibit the binding of H44L4 to immobilized purified α2bβ3. Figure 8B is a flow cytogram of platelets incubated with H44L4 in the presence of no peptide (curve 2), irrelevant peptide (curve 3), or inhibitory peptide "P4-12" (curve 4) followed by detection of H44L4 with phycoerythrin-labeled anti-human IgG. Platelets incubated with E1M2 (an irrelevant human monoclonal anti-Rh(D) antibody) is shown in curve 1.

Figure 9A is a chart showing representative scFvs, including the desmoglein specificity, heavy chain identifier, and light chain identifier. Figure 9B depicts the identification of each clone listed as a complete single chain variable fragment molecule (light chain of antibody followed by a glycine-rich linker indicated in boldface, followed by the heavy chain of the antibody).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of producing anti-desmoglein (Dsg) antibodies. The invention also includes anti-desmoglein antibodies (e.g., pathogenic or non pathogenic) as well as compositions and methods of identifying an anti-autoimmune reagent capable of binding to the anti-desmoglein antibody.

In another embodiment, the anti-desmoglien antibody targets Dsg1. Preferably, the anti-desmoglein antibody targets a calcium-binding transmembrane glycoprotein component of desmosomes. In some instances, Dsg1 comprises three desmoglein subfamily members that are members of the cadherin cell adhesion molecule superfamily. In another aspect, Dsg1 is located in a cluster on chromosome 18. In yet another aspect, Dsg1 is an autoantigen of the autoimmune skin blistering disease pemphigus foliaceus (PF).

The invention also provides methods and compositions for targeting anti-desmoglien antibodies. In one embodiment, the invention includes methods and compositions for targeting pathogenic antibodies associated with PF. Accordingly, the invention includes compositions and methods for modulating anti-desmoglein pathogenic antibodies using an inhibitor of anti-desmoglein pathogenic PF antibodies. The inhibitor of anti-desmoglein pathogenic PF antibodies is able to alleviate the pathology associated with the anti-desmoglein pathogenic PF antibody. In one aspect, the inhibitor is able to specifically bind to an anti-desmoglein pathogenic PF antibody and inhibit the biological activity of the anti-desmoglein pathogenic PF antibody. Inhibition of anti-desmoglein pathogenic PF antibodies can be achieved on the protein level, for example by contacting the pathogenic PF antibody with a binding partner. The binding partner can sequester, inhibit activity, or prevent the pathogenic PF antibody from otherwise binding to its cognate binding partner. For example, the pathogenic PF antibody can be inhibited with an anti-idiotypic antibody or a peptide (or other small molecule) that is capable of binding to the pathogenic PF antibody and inhibiting the biological activity of the pathogenic PF antibody.

In another aspect, the inhibition of the pathogenic PF antibody can be achieved at the genetic level. For example, inhibition of the pathogenic PF antibody can be achieved by inhibiting gene expression using for example small interfering RNA (siRNA), a microRNA, an antisense nucleic acid, a ribozyme, a polyamide, a triple-helix-forming agent, a synthetic peptide nucleic acids (PNAs), an agRNA, a LNA/DNA copolymer, and any combination thereof

The invention includes any method capable of inhibiting the biological activity of pathogenic PF antibodies. For example, any method of negatively regulating the expression or activity of the pathogenic PF antibody, including but not limited to transcription of the pathogenic antibody mRNA, stability of the pathogenic PF antibody mRNA, translation of the pathogenic PF antibody mRNA, stability of the pathogenic PF antibody, post-translational modifications of the pathogenic PF antibody, or any combination thereof, is encompassed in the invention.

This invention relates in one embodiment to compositions and methods for the use of an anti-autoimmune antibody, peptide, or small molecule that is specific against a pathogenic PF antibody whereby the pathogenic PF antibody is responsible for pemphigus foliaceus conditions. Accordingly, the invention includes anti-autoimmune reagents that target at least antibodies associated with PF.

The anti-autoimmune reagents of the invention are at least useful for targeting a B cell by way of contacting the anti-autoimmune reagent with the corresponding autoantibody expressed on the B cell.

The invention also includes the use of the anti-autoimmune reagents for diagnosing the pathology of pemphigus. In one aspect, the anti-autoimmune reagents are able to specifically bind to pathogenic PF antibodies and therefore reduce the number of false positive identification of pemphigus patients. This is because in some instances, the anti-autoimmune reagents of the present invention are more specific to pathogenic PF antibodies than the prior art reagents.

The invention also relates to the discovery that a number of non-pathogenic antibodies were identified from a PF patient. The non-pathogenic can be used to target therapeutic molecules to a specific site of interest in a mammal. Preferably, the mammal is a human. In an aspect of the invention, such antibodies are non-pathogenic to their target, e.g., target tissue.

Definitions

Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and nucleic acid chemistry and hybridization are those well known and commonly employed in the art.

Standard techniques are used for nucleic acid and peptide synthesis. The techniques and procedures are generally performed according to conventional methods in the art and various general references (e.g., Sambrook and Russell, 2001, Molecular Cloning, A Laboratory Approach, Cold Spring Harbor Press, Cold Spring Harbor, NY, and Ausubel et al., 2002, Current Protocols in Molecular Biology, John Wiley & Sons, NY), which are provided throughout this document.

The nomenclature used herein and the laboratory procedures used in analytical chemistry and organic syntheses described below are those well known and commonly employed in the art. Standard techniques or modifications thereof, are used for chemical syntheses and chemical analyses.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "about" as used herein means in quantitative terms plus or minus 5%, or in another embodiment plus or minus 10%, or in another embodiment plus or minus 15%, or in another embodiment plus or minus 20%.

The term "antibody," as used herein, refers to an immunoglobulin molecule which is able to specifically bind to a specific epitope on an antigen. Antibodies can be intact immunoglobulins derived from natural sources or from recombinant sources and can be immunoreactive portions of intact immunoglobulins. Some antibodies are typically tetramers of immunoglobulin molecules. The antibodies in the present invention may exist in a variety of forms including, for example, polyclonal antibodies, monoclonal antibodies, chimeric, hybrid, Fv, Fab and $F(ab)_2$, as well as single chain antibodies, primatized, and humanized antibodies. Antibody fragments refer to antigen-binding immunoglobulin peptides which are at least about 5 to about 15 amino acids or more in length, and which retain the capacity to bind to the antigen. (Harlow et al., 1999, Using Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, Antibodies: A Laboratory Manual, Cold Spring Harbor, New York; Houston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879-5883; Bird et al., 1988, Science 242:423-426).

An "antibody heavy chain," as used herein, refers to the larger of the two types of polypeptide chains present in all antibody molecules in their naturally occurring conformations.

An "antibody light chain," as used herein, refers to the smaller of the two types of polypeptide chains present in all antibody molecules in their naturally occurring conformations.

By the term "synthetic antibody" as used herein, is meant an antibody which is generated using recombinant DNA technology, such as, for example, an antibody expressed by a bacteriophage as described herein. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using synthetic DNA or amino acid sequence technology which is available and well known in the art.

As used herein, an "autoantibody" or an "autoimmune antibody" is an antibody produced by the immune system that is directed against one or more of the host's own proteins. Autoantibodies may be produced by a host's immune system when it fails to distinguish between "self" and "non-self" proteins. Usually the immune system is able to

discriminate by recognizing foreign substances ("non-self") and ignoring the host's own cells ("self"). When the immune system ceases to recognize one or more of the host's normal constituents as "self", it may produce autoantibodies that attack its own cells, tissues, and/or organs.

As used herein, an "anti-autoimmune reagent" refers to an agent that is capable of binding to an autoimmune antibody. An example of an autoimmune antibody is an anti-desmoglein antibody. Therefore, an anti-autoimmune reagent can be any agent that can bind to an anti-desmoglein antibody. In some instances, the anti-autoimmune reagent is an antibody that can bind to an anti-desmoglein antibody. In another aspect, the anti-autoimmune reagent is a peptide, polypeptide or other small molecule that can bind to an anti-desmoglein antibody.

By the term "Fab/phage" as used herein, is meant a phage particle which expresses the Fab portion of an antibody.

By the term "scFv/phage" as used herein, is meant a phage particle which expresses the Fv portion of an antibody as a single chain.

"Phage," or "phage particle," as these terms are used herein, include bacteriophage that contain phage nucleic acid encoding, *inter alia*, an antibody. This is because, as would be appreciated by the skilled artisan, unlike peptide phage display (where the peptide DNA insert is small and it is actually cloned into the phage DNA), the larger scFv or Fab DNA inserts are actually cloned into, among other things, a plasmid. Thus, the nucleic acid encoding the antibody, *e.g.*, a plasmid such as, but not limited to, pComb3X, not only comprises a plasmid origin of replication, but also a phage (*e.g.*, M13) origin of replication sequence and an M13 packaging sequence, so that when the nucleic acid is produced, a helper phage can be used to provide the required phage (*e.g.*, M13) proteins *in trans* to make "phage-like" particles. That is, these particles resemble phage on the outside, but on the inside they contain plasmid (also referred to as a "phagemid") DNA. In other words, the phagemid DNA need not encode any M13 phage proteins, except a piece of M13 gene III fused to the DNA for antibody or peptide. Thus, it should be understood that the terms "phage," "phage particle," "phage-like particle" and "phagemid" are used interchangeably herein.

As used herein, to "alleviate" a disease, disorder or condition means reducing the severity of one or more symptoms of the disease, disorder or condition.

"Derivative" in the context of proteins and peptides includes any purposefully generated amino acid sequence that in its entirety, or in part, comprises a substantially

similar amino acid sequence to a desired protein. The term derivative can also be applied to the antibodies described herein such that "derivative" includes any purposefully generated peptide, which in its entirety, or in part, comprises a substantially similar amino acid sequence to an anti-desmoglein antibody or an anti-idiotypic antibody that is capable of specifically bindng to an anti-desmoglein antibody. Derivatives of the antibodies may be characterized by single or multiple amino acid substitutions, deletions, additions, or replacements. Derivatives may include: (a) derivatives in which one or more amino acid residues are substituted with conservative or non-conservative amino acids; (b) derivatives in which one or more amino acids are added; (c) derivatives in which one or more of the amino acids of the amino acid sequence includes a substituent group; (d) derivatives in which amino acid sequences or a portion thereof is fused to another peptide (*e.g.*, serum albumin or protein transduction domain); (e) derivatives in which one or more nonstandard amino acid residues (*e.g.*, those other than the 20 standard L-amino acids found in naturally occurring proteins) are incorporated or substituted into the amino acid sequences; (f) derivatives in which one or more non-amino acid linking groups are incorporated into or replace a portion of the amino acids; and (g) derivatives in which one or more amino acid is modified by glycosylation, acetylation, myristoylation, and the like.

"Immunization" is the process of administering an immunogenic composition and stimulating an immune response to an antigen in a host (*i.e.*, rodents and rabbits). Preferred hosts are mammals, such as primates (*e.g.*, humans) as well as veterinary animals and agricultural animals. An "immunogen" is an immunogenic composition used to immunized the host. "Immunogen" also refers to a substance that is able to stimulate or induce a humoral antibody and/or cell-mediated immune response in a mammal. In some instances, the immunogen comprises an anti-desmoglein pathogenic antibody or any fragment thereof.

An "immune response" refers to the activities of the immune system, including activation and proliferation of specific cytotoxic T-cells and B-cells resulting in antigen-specific antibody production, after contact with an antigen.

The term "expression" as used herein is defined as the transcription and/or translation of a particular nucleotide sequence driven by its promoter.

The term "expression vector" as used herein refers to a vector containing a nucleic acid sequence coding for at least part of a gene product capable of being transcribed. In some cases, RNA molecules are then translated into a protein, polypeptide, or peptide. In other cases, these sequences are not translated, for example, in the production of antisense

molecules, siRNA, ribozymes, and the like. Expression vectors can contain a variety of control sequences, which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operatively linked coding sequence in a particular host organism. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well.

As used herein, the term "fragment," as applied to a nucleic acid, refers to a subsequence of a larger nucleic acid. A "fragment" of a nucleic acid can be at least about 15 nucleotides in length; for example, at least about 50 nucleotides to about 100 nucleotides; at least about 100 to about 500 nucleotides, at least about 500 to about 1000 nucleotides; at least about 1000 nucleotides to about 1500 nucleotides; about 1500 nucleotides to about 2500 nucleotides; or about 2500 nucleotides (and any integer value in between).

As used herein, the term "fragment," as applied to a protein or peptide, refers to a subsequence of a larger protein or peptide. A "fragment" of a protein or peptide can be at least about 20 amino acids in length; for example, at least about 50 amino acids in length; at least about 100 amino acids in length; at least about 200 amino acids in length; at least about 300 amino acids in length; or at least about 400 amino acids in length (and any integer value in between).

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

Moreover, nucleic acid molecules encoding proteins from other species (homologs), which have a nucleotide sequence which differs from that of the human proteins described herein are within the scope of the invention. Nucleic acid molecules corresponding to natural allelic variants and homologs of a cDNA of the invention can be isolated based on their identity to human nucleic acid molecules using the human cDNAs, or a portion thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

An "isolated nucleic acid" refers to a nucleic acid segment or fragment which has been separated from sequences which flank it in a naturally occurring state, *e.g.*, a DNA fragment which has been removed from the sequences which are normally adjacent to the fragment, *e.g.*, the sequences adjacent to the fragment in a genome in which it naturally occurs. The term also applies to nucleic acids which have been substantially purified from other components which naturally accompany the nucleic acid, *e.g.*, RNA or DNA or proteins, which naturally accompany it in the cell. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote, or which exists as a separate molecule (*e.g.*, as a cDNA or a genomic or cDNA fragment produced by PCR or restriction enzyme digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence.

In the context of the present invention, the following abbreviations for the commonly occurring nucleic acid bases are used. "A" refers to adenosine, "C" refers to cytidine, "G" refers to guanosine, "T" refers to thymidine, and "U" refers to uridine.

A "polynucleotide" means a single strand or parallel and anti-parallel strands of a nucleic acid. Thus, a polynucleotide may be either a single-stranded or a double-stranded nucleic acid.

The term "nucleic acid" typically refers to large polynucleotides.

The term "oligonucleotide" typically refers to short polynucleotides, generally, no greater than about 50 nucleotides. It will be understood that when a nucleotide sequence is represented by a DNA sequence (*i.e.*, A, T, G, C), this also includes an RNA sequence (*i.e.*, A, U, G, C) in which "U" replaces "T."

Conventional notation is used herein to describe polynucleotide sequences: the left-hand end of a single-stranded polynucleotide sequence is the 5'-end; the left-hand direction of a double-stranded polynucleotide sequence is referred to as the 5'-direction.

The direction of 5' to 3' addition of nucleotides to nascent RNA transcripts is referred to as the transcription direction. The DNA strand having the same sequence as an mRNA is referred to as the "coding strand"; sequences on the DNA strand which are located 5' to a reference point on the DNA are referred to as "upstream sequences"; sequences on the DNA strand which are 3' to a reference point on the DNA are referred to as "downstream sequences."

As used herein, the term "modulate" is meant to refer to any change in biological state, i.e. increasing, decreasing, and the like. For example, the term "modulate"

refers to the ability to regulate positively or negatively the expression or activity of, for example, an anti-desmoglein pathogenic antibody, including but not limited to transcription of the desired anti-desmoglein pathogenic antibody mRNA, stability of the desired anti-desmoglein pathogenic antibody mRNA, translation of the desired anti-desmoglein pathogenic antibody mRNA, stability of the desired anti-desmoglein pathogenic antibody polypeptide, post-translational modifications of the desired anti-desmoglein pathogenic antibody, or any combinations thereof. Further, the term modulate can be used to refer to an increase, decrease, masking, altering, overriding or restoring of activity of an anti-desmoglein pathogenic antibody.

A "portion" of a polynucleotide means at least about twenty sequential nucleotide residues of the polynucleotide. It is understood that a portion of a polynucleotide may include every nucleotide residue of the polynucleotide.

"Polypeptide" refers to a polymer composed of amino acid residues, related naturally occurring structural variants, and synthetic non-naturally occurring analogs thereof linked via peptide bonds, related naturally occurring structural variants, and synthetic non-naturally occurring analogs thereof. Synthetic polypeptides can be synthesized, for example, using an automated polypeptide synthesizer. The term "protein" typically refers to large polypeptides. The term "peptide" typically refers to short polypeptides. Conventional notation is used herein to portray polypeptide sequences: the left-hand end of a polypeptide sequence is the amino-terminus; the right-hand end of a polypeptide sequence is the carboxyl-terminus. As used herein the term polypeptide is mutually inclusive of the terms "peptides" and "proteins".

A "recombinant polypeptide" is one which is produced upon expression of a recombinant nucleic acid.

By the term "specifically binds," as used herein, is meant a compound, *e.g.*, a protein, a nucleic acid, an antibody, and the like, which recognizes and binds a specific molecule, but does not substantially recognize or bind other molecules in a sample.

The term "subject" refers in one embodiment to a mammal including a human in need of therapy for, or susceptible to, a condition or its sequelae. The subject may include dogs, cats, pigs, cows, sheep, goats, horses, rats, and mice and humans. The term "subject" does not exclude an individual that is normal in all respects.

As used herein, to "treat" means reducing the frequency with which symptoms of a disease, disorder, or adverse condition, and the like, are experienced by a patient. Such non-limiting conditions include bona fide illness as well as cosmetic or other

conditions for example removal of unwanted hair or treating baldness where hair growth is desired.

A molecule (e.g., a ligand, a receptor, an antibody, and the like) "specifically binds with" or "is specifically immunoreactive with" another molecule where it binds preferentially with the compound and does not bind in a significant amount to other compounds present in the sample.

As used herein, a "therapeutic agent" is a molecule or atom, which is conjugated to an anti-autoimmune reagent to produce a conjugate which is useful for therapy. Examples of therapeutic agents include drugs, toxins, enzymes, hormones, cytokines, immunomodulators, anti-tumor agents, chemotherapeutic agents, anti-cell proliferation agents, boron compounds, and therapeutic radioisotopes.

"Therapeutic plasmapheresis" is herein meant as a method for removing toxic or unwanted elements, for example, plasma constituents implicated in disease, such as complement or autoantibodies, from the blood of a patient. In one embodiment, the invention provides a method for removing blood from a patient, separating the plasma, filtering the unwanted elements from the plasma, such as plasma constituents implicated in disease, such as complement or autoantibodies, and reinfusing the plasma replacement back to the patient, wherein the filtering step utilizes an anti-autoimmune reagent of the invention to remove pathogenic autoantibodies from the blood sample.

Description of the Invention

Pemphigus is an autoimmune blistering disease of the skin. Pemphigus foliaceus (PF) is characterized in some aspects by the presence of autoantibodies against Dsg1, which cause blistering of the skin, but not mucous membranes, due to loss of cell adhesion in the superficial epidermis. The present invention relates to the isolation of both pathogenic and non-pathogenic using phage display technology from a PF patient.

In one embodiment, the provides a non-pathogenic antibody comprising a heavy chain encoded by VH1-18 gene, VH1-08 gene, VH3-09 gene, VH4-b gene, or VH3-66 gene. In another embodiment, the present invention provides a pathogenic antibody comprising a heavy chain encoded by VH3-07 gene, VH3-30 gene, or VH3-53 gene. The pathogenic PF antibodies share a conserved sequence at the amino acid level. The consensus sequence shared among the pathogenic PF antibodies resides in the CDR3 region of the antibody. The consensus sequence shared among the pathogenic PF antibodies is D/E-X-X-

X-W, wherein X can represent any amino acid. D-X-X-X-W is set forth in SEQ ID NO: 259. E-X-X-X-W is set forth in SEQ ID NO: 260).

The invention also provides a method of targeting pathogenic PF antibodies. For example, the pathogenic PF antibodies can be used to screen peptides or other small molecules for specific binding to the pathogenic PF antibody. Preferably, the pathogenic PF antibody is an anti-desmoglein antibody. Accordingly, the invention also provides an anti-autoimmune reagent capable of binding to a pathogenic PF antibody. In some instances, the anti-autoimmune reagent is an antibody that can bind to a desired pathogenic PF antibody.

In another embodiment, the present invention provides a method of analyzing PF in a model animal, comprising the steps of: administering a pathogenic human anti-Dsg1 antibody, comprising a heavy chain encoded by a VH3-07 gene, VH3-30 gene, and/or VH3-53 gene to a model animal; and analyzing PF progression and/or pathogenesis in a model animal, thereby analyzing PF in a model animal.

Anti-desmoglein Pathogenic Antibodies:

The present invention relates, in part, to the isolation of an anti-desmoglein pathogenic antibody from a PF patient. In one aspect, an anti-desmoglein pathogenic antibody can bind to Dsg1, but not to Dsg3. In yet another aspect, an anti-desmoglein pathogenic binds to both Dsg1 and Dsg3.

In another embodiment, the anti-Dsg pathogenic autoantibody used in the methods and compositions provided herein, is an anti-Dsg1 autoantibody. In another embodiment the anti-Dsg pathogenic autoantibody is an anti-Dsg_1 and anti-Dsg_3 autoantibody (Anti-$Dsg_{1,3}$ autoantibody). In one embodiment, the anti-Dsg pathogenic autoantibody is pathognomonic of pemphigus foliaceus (PF).

In one embodiment, the genetic analysis of cloned antibodies from the PF library show a restriction of autoantibody variable heavy (V_H) gene usage, with different V_H gene usage by pathogenic and non-pathogenic antibodies. In another embodiment, PF mAb V_H gene usage correlates with antibody function, with respect to Dsg antigen binding in one embodiment, or its pathogenicity in another embodiment. In one embodiment, genetic restriction in the light chain repertoire indicates functional importance. In one embodiment, limited genetic diversity in PF mAbs indicates it is feasible to improve the specificity and safety of pemphigus therapies by targeting the anti-Dsg antibodies, as opposed to generally suppressing the immune system.

In one embodiment, the V_H of the anti-desmoglein pathogenic autoantibody, against which the anti-autoimmune antibodies described in the methods and compositions provided herein are used, is encoded by VH3-07, VH3-30, VH3-53 or any combination thereof.

In another embodiment, a pathogenic antibody of the invention blocks at least about 30% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 40% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 50% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 55% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 60% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 65% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 70% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 75% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 80% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 85% of PF patient serum binding to Dsg1. In another embodiment, a pathogenic antibody of the invention blocks at least about 90% of PF patient serum binding to Dsg1.

In another embodiment, pathogenic antibody response among patients with PF is limited and directed at similar or identical epitopes on Dsg1. In another embodiment, a pathogenic antibody of the present invention binds to epitopes that are located in the amino-terminus of Dsg1. In another embodiment, a pathogenic antibody of the present invention binds to epitopes in an area that includes the trans-adhesive interface. In another embodiment, a pathogenic antibody of the present invention binds to conformational epitopes. In another embodiment, a pathogenic antibody of the present invention binds to calcium-stabilized epitopes.

In another embodiment, the non-pathogenic and pathogenic anti-Dsg1 correlated with their heavy chain gene usage. Very restricted heavy chain gene usage, limited to only five genes, characterized the anti-Dsg1 antibodies. In another embodiment, only certain light chains are permissive for Dsg1 binding.

In another embodiment, the present invention provides antibodies that bind the precursor protein of Dsg1. In another embodiment, the present invention provides that antibodies that bind the precursor protein of Dsg1 do not bind the mature protein.

In one embodiment, the pathogenic antibodies share a conserved sequence at the amino acid level. The consensus sequence shared among the pathogenic antibodies resides in the CDR3 region of the antibody. The consensus sequence shared among the pathogenic antibodies is D/E-X-X-X-W, wherein X can represent any amino acid.

The consensus sequence of D/E-X-X-X-W identified with the pathogenic cloned antibodies represents a structural binding motif that is believed to be a candidate for targeted therapy. Without wishing to be bound by any particular theory, it is believed that the consensus sequence of D/E-X-X-X-W may mimic the desmosomal cadherin tertiary structure, thereby directly (sterically) interfering with desmosomal trans-adhesion between cells.

Thus, the invention encompasses small molecules or peptidomimetic compounds that are able to inhibit the binding of an antibody comprising the D/E-X-X-X-W consensus sequence to its target sequence. Accordingly, the invention includes inhibitors based on the peptide sequences of D/E-X-X-X-W, as well as to methods of making them.

A preferred peptide interferes with at least the activity of a pathogenic anti-desmoglein antibody mediated by the D/E-X-X-X-W consensus sequence. The skilled person is aware that a peptidomimetic compound can be made in which one or more amino acid residues is replaced by its corresponding D-amino acid, substitutions or modifications are made to one or more amino acids in the sequence, peptide bonds can be replaced by a structure more resistant to metabolic degradation and different cyclizing constraints and dimerization groups can be incorporated.

With respect to compounds in which one or more amino acids is replaced by its corresponding D-amino acid, the skilled person is aware that retro-inverso amino acid sequences can be synthesized by standard methods; see, for example, Chorev and Goodman, 1993 Acc. Chem. Res. 26: 266. Olson et al., 1993 J. Med. Chem. 36: 3039 provides an example of replacing a peptide bond with a structure more resistant to metabolic degradation.

Peptidomimetic compounds can also be made where individual amino acids are replaced by analogous structures, for example gem-diaminoalkyl groups or alkylmalonyl groups, with or without modified termini or alkyl, acyl or amine substitutions to modify their charge. The use of such alternative structures can provide significantly longer half-life in the body, since they are more resistant to breakdown under physiological conditions.

Methods for combinatorial synthesis of peptide analogs and for screening of peptides and peptide analogs are well known in the art (see, for example, Gallop et al., 1994 J. Med. Chem. 37: 1233). It is particularly contemplated that the compounds of the invention are useful as templates for design and synthesis of compounds of improved activity, stability and bioavailability. Preferably where amino acid substitution is used, the substitution is conservative, i.e. an amino acid is replaced by one of similar size and with similar charge properties. As used herein, the term "conservative substitution" denotes the replacement of an amino acid residue by another, biologically similar residue. Examples of conservative substitutions include the substitution of one hydrophobic residue such as isoleucine, valine, leucine, alanine, cysteine, glycine, phenylalanine, proline, tryptophan, tyrosine, norleucine or methionine for another, or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic acid for aspartic acid, or glutamine for asparagine, and the like. Neutral hydrophilic amino acids which can be substituted for one another include asparagine, glutamine, serine and threonine. The term "conservative substitution" also includes the use of a substituted amino acid in place of an unsubstituted parent amino acid.

Phage Display

The antibodies of the present invention include those cloned from a phage antibody library, as described in detail elsewhere herein. For example, a cDNA library is generated from mRNA obtained from a population of antibody-producing cells. The mRNA encodes rearranged immunoglobulin genes and thus, the cDNA encodes the same. Amplified cDNA is cloned into M13 expression vectors creating a library of phage which express human Fab or scFv fragments on their surface. Phage which display the antibody of interest are selected by antigen binding and are propagated in bacteria to produce soluble human Fab or scFv immunoglobulin. Thus, in contrast to conventional monoclonal antibody synthesis, this procedure immortalizes DNA encoding human immunoglobulin rather than cells which express human immunoglobulin.

In one embodiment, the methods of the present invention provide utilizing antibody phage display on a Dsg1 thus isolating anti-Dsg1 antibodies. In another embodiment, using the phage display technique results in the isolation of anti- Dsg1 scFv mAbs.

Phage display libraries allow for the in vitro identification of human antibody products directed against molecular targets. In one embodiment, the methods of the present

invention provide that phage display libraries enable the in vitro identification of human antibody products directed against an isolated Dsg1 protein or fragment thereof.

Antibody phage display of the present invention provides the linkage between genotype and phenotype. In another embodiment, selection of phage clones of the present invention is based on binding affinity. In another embodiment, selection of phage clones of the present invention is based on binding specificity. In another embodiment, selection of phage clones of the present invention is based on functional activity of the displayed antibody (phenotype). In another embodiment, selection of phage clones of the present invention is based on binding affinity, specificity, and functional activity of the displayed antibody (phenotype). Each phage carries the DNA for the antibody it displays on its surface, the phenotype is directly linked to the antibody genotype (cDNA sequence). This enables rapid selection of clones displaying antibody chains with desirable characteristics with desirable affinity to a target antigen.

In another embodiment, the present invention provides a high affinity human antibody which is specific for Dsg1. In another embodiment, the present invention provides that light chain shuffling while retaining the heavy chain variable region using phage display technology is able to modify the ultrafine specificity of the antigen-binding construct. In another embodiment, the present invention provides that heavy chain shuffling while retaining the light chain variable region using phage display technology is able to modify the ultrafine specificity of the antigen-binding construct. In another embodiment, the present invention provides that heavy chain promiscuity is limited in in vivo developed antibodies. In another embodiment, the present invention provides that light chain promiscuity is limited in in vivo developed antibodies. In another embodiment, the present invention allows such to form antigen-binding structures following random assortment of heavy and light chain variable regions. In another embodiment, the present invention provides that phage display technology selects against clones which are restricted with respect to light chain usage. In another embodiment, the present invention provides that phage display technology selects against clones which are restricted with respect to heavy chain usage. In another embodiment, the present invention provides that phage display technology represents a population which is restricted in this respect.

In another embodiment, the present invention provides isolation of non-pathogenic anti-Dsg1 scFvs from a PF patient. Peripheral blood lymphocytes from a patient with active PF are used to construct a library in which each phage particle displays a scFv antibody fragment on its surface and contains the cDNA encoding the heavy and light chain

variable regions for that particular scFv within. In another embodiment, the library is screened by multiple rounds of panning as described hereinabove on immobilized, baculovirus-produced Dsg1. In another embodiment, the library is screened by multiple rounds of panning as described hereinabove on immobilized, baculovirus-produced Dsg1using standard ELISA plate panning methods known to one skilled in the art.

In another embodiment, selection of clones is based upon methods which provide that after an initial screening, unique clones are isolated based on their heavy and light chain nucleotide sequences. For example, some of the clones are derived from heavy chain genes VH1-18 and VH3-09. In some instances, the clones derived from heavy chain genes VH1-18 and VH3-09 used multiple light chain genes. In some instances, clones comprising heavy chain genes VH1-18 and VH3-09 produce antibodies that are non-pathogenic (see table 1).

In another embodiment, the methods of the present invention provide that the diversity of the selected clones is increased in order to find pathogenic antibodies. The methods provide that an antibody phage library is tested again by a second panning procedure on baculovirus-produced Dsg1 ELISA plates. The methods of the present invention provide that in the second round of panning additional non-pathogenic clones are uncovered.

In another embodiment, the methods of the present invention provide isolating pathogenic anti-Dsg1 antibodies by non-pathogenic epitope blocking utilized in concert with phage display. In another embodiment, the methods of the present invention provide that blocking to mask non-pathogenic epitopes results in obtaining pathogenic antibody clones. The methods of the present invention further provide isolation of pathogenic anti-Dsg1 scFvs using a non-pathogenic epitope blocking approach. The panning strategy is to target the isolation of pathogenic clones that are putative low abundant clones by blocking non-pathogenic epitopes. The blocking of non-pathogenic epitopes is preformed using a set of previously-isolated non-pathogenic clones.

Using the "non-pathogenic epitope blocking" approach, additional unique clones are isolated. In some instances, pathogenic clones are isolated using this technique. In some instances, the pathogenic clones are encoded by heavy chain genes not previously seen in the set of non-pathogenic anti-Dsg1 antibodies. In another embodiment, the methods of the present invention provide that pathogenic clones are encoded by heavy chain genes VH3-07, VH3-30, or VH3-53. In some instances, the clones derived from heavy chain genes

VH3-07 and VH3-30 used multiple light chain genes. In some instances, clones comprising heavy chain genes VH3-07, VH3-30, and VH3-53 produce antibodies that are pathogenic.

In one aspect of the invention, the antibody comprises a heavy chain sequence selected from the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof. In another aspect, the antibody comprisies a heavy chain encoded by the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 130-172, and any combination thereof. In another aspect of the invention, the antibody comprises a light chain sequence selected from the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof. In another aspect, the antibody comprisies a light chain encoded by the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 87-129, and any combination thereof. In another aspect of the invention, the antibody comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 44-86, and any combination thereof. In another aspect, the antibody comprisies the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-43, and any combination thereof.

Using the information provided herein, the antibodies of the present invention can be produced recombinantly using standard techniques well known to those of skill in the art. For example, the sequences provided herein can be used to identify and clone appropriate nucleic acid sequences encoding the antibodies. These nucleic acid sequences can then be used to express one or more antibodies. The nucleic acid sequence may be optimized to reflect particular codon "preferences" for various expression systems according to standard methods well known to those of skill in the art.

Using the sequence information provided herein, the nucleic acids may be synthesized according to a number of standard methods known to those of skill in the art. Oligonucleotide synthesis, is preferably carried out on commercially available solid phase oligonucleotide synthesis machines or manually synthesized using the solid phase phosphoramidite triester method described by Beaucage et. al., 1981, Tetrahedron Letts. 22:1859-1862.

Once a nucleic acid encoding an antibody is synthesized, it may be amplified and/or cloned according to standard methods in order to produce recombinant antibodies of the invention. Molecular cloning techniques to achieve these ends are known in the art. A wide variety of cloning and *in vitro* amplification methods suitable for the construction of recombinant nucleic acids are known to those skilled in the art. Examples of these techniques and instructions sufficient to direct the skilled artisan are found in Berger and

Kimmel, Guide to Molecular Cloning Techniques, Methods in Enzymology volume 152 Academic Press, Inc., San Diego, Calif. (Berger); Sambrook et al., 2002 Molecular Cloning. A Laboratory Manual Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY, (Sambrook). Methods of producing recombinant immunoglobulins are also known in the art. See, Cabilly, U.S. Pat. No. 4,816,567; and Queen et al., 1989 Proc. Nat'l Acad. Sci. USA 86:10029-10033.

Examples of techniques sufficient to direct persons of skill through *in vitro* amplification methods, including the polymerase chain reaction (PCR), the ligase chain reaction (LCR), and other DNA or RNA polymerase-mediated techniques are found in Berger, Sambrook, and Ausubel, as well as U.S. Pat. No. 4,683,202 and U.S. Pat. No. 5,426,039.

Once the nucleic acid encoding a desired antibody is isolated and cloned, a skilled artisan may express the recombinant gene(s) in a variety of engineered cells known to those of skill in the art. Examples of such cells include bacteria, yeast, filamentous fungi, insect (especially employing baculoviral vectors), and mammalian cells. It is expected that those of skill in the art are knowledgeable in the numerous expression systems available for expression of the desired antibodies.

For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use chimeric, hybrid, primatized, humanized, or human antibodies. Methods for producing chimeric and hybrid antibodies are known in the art. *See e.g.*, Morrison, 1985 *Science* 229: 1202-1207; U.S. Pat. Nos. 6,965,024, 5,807,715; 4,816,567; and 4,816,397. Humanized antibodies are antibody molecules from non-human species that bind the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and framework regions and constant domains from a human immunoglobulin molecule. Often, framework residues in the human framework regions are substituted with the corresponding residue from the CDR donor antibody to alter and in some instances improve, antigen binding. These framework substitutions are identified by methods well known in the art, *e.g.*, by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. *See, e.g.*, Queen et al., U.S. Pat. No. 5,585,089. Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting and chain shuffling. Humanized antibodies may be generated using any of the

methods disclosed in U.S. Pat. No. 5,693,762, U.S. Pat. No. 5,693,761, U.S. Pat. No. 5,585,089, U.S. Pat. No. 6,180,370.

Screening for anti-autoimmune reagents

The present invention is partly based on the identification of peptides or small molecules that bind a desired autoimmune antibody. In some instances, the autoimmune antibody is a disease associate-pathogenic antibody, for example a pathogentic anti-desmoglein antibody. Accordingly, a peptide that binds to a disease associated-pathogenic antibody is an example of an anti-autoimmune reagent. However, the invention also includes peptides or small molecules that bind to non-pathogenic antibodies.

There are several examples of methods that use peptides or nucleotides to develop libraries of potential receptor, enzyme, or antibody interacting peptides. These libraries have been incorporated into systems that allow the expression of random peptides on the surface of different phage or bacteria. The use of phage display technology to produce and screen libraries of polypeptides for binding to a selected target has been widely used. A basic concept of phage display methods is the establishment of a physical association between DNA encoding a polypeptide to be screened and the target polypeptide. This physical association is provided by the phage particle, which displays a polypeptide as part of a capsid enclosing the phage genome which encodes the polypeptide. The establishment of a physical association between polypeptides and their genetic material allows simultaneous mass screening of very large numbers of phage bearing different polypeptides. Phage displaying a polypeptide with affinity to a target bind to the target and these phage are enriched by affinity screening to the target. The identity of polypeptides displayed from these phage can be determined from their respective genomes. Using these methods a polypeptide identified as having a binding affinity for a desired target can then be synthesized in bulk by conventional means.

In one embodiment, the binding of an anti-autoimmune reagent correlates with V_H gene usage. In one embodiment, PF mAb V_H genes identified by phage display represent feasible targets for therapy. These genes are VH3-07, VH3-30, VH3-53, or the combinations thereof. In another embodiment, certain combination of otherwise non-pathogenic anti-Dsg antibodies, still induce pathogenic reaction in the subject. Accordingly, in one embodiment PF mAb V_H target gene for therapy using the compositions and methods provided herein is VH1-18, VH1-08, VH3-09, VH4-b, VH3-66 gene or their combination in other embodiments.

The present invention comprises systems for screening and/or testing the ability of a candidate compound to bind an anti-Dsg1 antibody of the invention. In some instances, a candidate compound that binds pathogenic human monoclonal ScFv anti-Dsg1 antibodies also binds anti-Dsg1 antibodies derived from a PF patient. Preferably, a candidate compound that binds pathogenic human monoclonal ScFv anto-Dsg1 antibodies also binds anti-Dsg1 antibodies in vivo. More preferably, a candidate compound that binds pathogenic human monoclonal ScFv anto-Dsg1 antibodies also binds anti-Dsg1 antibodies in a PF patient. In some instances, the candidate compound inhibits binding of pathogenic antibodies to their epitopes.

The candidate compound of the present invention is a peptide. In another embodiment, the candidate compound of the present invention is a protein. In another embodiment, the candidate compound of the present invention is an inorganic compound. In another embodiment, the candidate compound of the present invention is an organic compound. In another embodiment, the candidate compound of the present invention mimics a Dsg1 pathogenic epitope. In another embodiment, a candidate compound of the present invention comprises a Dsg1 pathogenic epitope.

However, the invention also contemplates peptides and small moleuces that bind to non-pathogenic antibodies. This is because a non-pathogenic can be used in the phage display library screening procedure to identify the corresponding binding molecule, and in some cases non-pathogenic antibodies when used in combination or under certain conditions may prove to cause pathology.

Inhibitors of Anti-Desmoglein Pathogenic Antibodies:

The invention provides a composition comprising an anti-autoimmune reagent. The anti-autoimmune reagent includes any agent that is capable of binding to or inhibiting the expression of an autoimmune antibody. In one aspect, the anti-autoimmune reagent is an antibody that binds to an autoantibody. In another aspect, the anti-autoimmune reagent is a peptide or small molcule that binds to an autoantibody. For example, the anti-autoimmune reagent binds to a pathogenic anti-desmoglein antibody.

Binding function:

The present invention relates to the discovery that inhibition of an anti-desmoglein pathogenic antibody provides a therapeutic benefit. Accordingly, the invention includes an inhibitor of an anti-desmoglein pathogenic antibody. In one aspect, the inhibitor

is an agent capable of binding and sequestering an anti-desmoglein pathogenic antibody. In another aspect, the inhibitor can inhibit the function an anti-desmoglein pathogenic autoantibody. In yet another aspect, the inhibitor can inhibit the expression of an anti-desmoglein pathogenic antibody.

In another embodiment, the inhibitor is an anti-autoimmune reagent that is capable of binding to an anti-desmoglein pathogenic antibody. The anti-autoimmune reagent can be an antibody that binds to an anti-desmoglein pathogenic antibody whereby the anti-autoimmune reagent (e.g., an antibody) can be produced by immunizing an animal (*i.e.*, rodents or rabbits) with an immunogen comprising anti-desmoglein pathogenic antibody or any fragment thereof.

In one embodiment, the specific antibody-targeted therapy for pemphigus aims to suppress or eliminate only the anti-Dsg autoantibodies. In another embodiment, the methods described herein target only the pathogenic autoantibodies. In one embodiment, antibodies are targeted by their idiotype. In another embodiment, antibodies are targeted based on their variable region gene usage.

In one embodiment, cloning of human PF mAbs provide novel strategies for direct antibody targeting. In another embodiment treatments using the methods provided herein, are designed based on autoantibody V_H gene usage. In another embodiment, the identification of peptides that specifically bind PF mAbs indicates that the small molecule reagents can also discriminate among PF mAbs based on their V_H gene usage. These small molecule reagents are more practical in one embodiment, than rabbit antibodies against PF mAbs for the development of therapeutic intervention strategies.

Accordingly, the invention provides a method of inhibiting the binding of a autoimmne antibody, for example a pathogenic autoimmune antibody to desmoglein (Dsg), comprising contacting the autoimmune antibodies with a composition comprising an agent capable of inhibiting the expression or function of a variable region of an anti-desmoglein pathogenic autoantibody. In another embodiment, the anti-desmoglein (Dsg) pathogenic autoantibody is an anti-Dsg1 autoantibody, an anti-Dsg3 autoantibody, or an anti-Dsg_1 and anti-Dsg_3 autoantibody (Anti-$Dsg_{1,3}$ autoantibody), which, in yet another embodiment, is pathognomonic of pemphigus foliaceus (PF).

In another embodiment, provided herein is a method of inhibiting the binding of a pathogenic autoimmune antibody to desmoglein (Dsg), comprising contacting the autoimmune antibodies with a composition comprising an anti-autoimmune reagent capable of inhibiting the binding of a variable region of an anti-desmoglein pathogenic autoantibody.

Preferably, the gene encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody, is VH3-07, VH3-30, VH3-53, or the combinations thereof in other embodiments.

In one embodiment, the antibody-targeted agents described in the compositions provided herein and utilized in the methods provided herein, could be coupled to columns as an adjunct for plasmapheresis to improve the efficiency of pathogenic antibody removal from subjects' sera. In another embodiment, the antibody-specific agents described in the compositions provided herein and utilized in the methods provided herein, are linked to B cell superantigens as a method of V_H-targeted B-cell deletion. In one embodiment, the methods provided herein offer a safer and more effective treatments for pemphigus. In another embodiment, the V_H gene-targeting approach described hereinabove has implications for the treatment of other genetically restricted antibody-mediated diseases.

Inhibiting expression:

In one embodiment, the inhibitor used in the compositions provided herein, which are utilized in the methods provided herein, is capable of inhibiting the expression of a nucleotide sequence encoding the heavy chain (V_H) of an anti-desmoglein autoantibody. In another embodiment, the nucleotide sequence to be inhibited is selected from the group consisting of the sequence set forth in SEQ ID NOs: 130-172, and any combination thereof.

In another embodiment, the agent used in the compositions provided herein, which are utilized in the methods provided herein, is capable of inhibiting the expression of a nucleotide sequence encoding the light chain (V_L) of an anti-desmoglein autoantibody. In another embodiment, the nucleotide sequence to be inhibited is selected from the group consisting of the sequence set forth in SEQ ID NOs: 87-129, and any combination thereof.

In yet another embodiment, the agent used in the compositions provided herein, which are utilized in the methods provided herein, is capable of inhibiting the expression of a nucleotide sequence encoding an anti-desmoglein autoantibody. In another embodiment, the nucleotide sequence to be inhibited is selected from the group consisting of the sequence set forth in SEQ ID NOs: 1-43, and any combination thereof.

In one embodiment, the nucleotide has at least 85% homology to the nucleotide sequence selected from the group consisting of the sequence set forth in SEQ ID NOs. 1-43, 87-129, 130-172, and any combination thereof. In one embodiment, the terms "homology", "homologue" or "homologous", indicate that the sequence referred to, whether an amino acid sequence, or a nucleic acid sequence, exhibits, in one embodiment at least 70

% correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 72 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 75 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 80 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 82 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 85 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 87 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 90 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 92 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 95 % or more correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 97% correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits at least 99 % correspondence with the indicated sequence. In another embodiment, the amino acid sequence or nucleic acid sequence exhibits 95 % - 100 % correspondence with the indicated sequence. Similarly, as used herein, the reference to a correspondence to a particular sequence includes both direct correspondence, as well as homology to that sequence as herein defined.

In one embodiment, the agent used in the compositions described herein, which are utilized in the methods provided herein, is a siRNA. In another embodiment, the agent capable of inhibiting the expression of the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody is a polyamide. In another embodiment, the agent capable of inhibiting the expression of the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody is a triple-helix-forming agent. In another embodiment, the agent capable of inhibiting the expression of the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody is an antisense RNA. In another embodiment, the agent capable of inhibiting the expression of the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody is a synthetic peptide nucleic acids (PNAs). In another embodiment, the agent capable of inhibiting the expression of the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody is an agRNA. In another embodiment, the agent capable of

inhibiting the expression of the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody is a LNA/DNA copolymer. In another embodiment, the agent capable of inhibiting the expression of the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody is a small molecule chemical compounds, or a combination thereof.

In one embodiment, the term "siRNA" refers to RNA interference, which in another embodiment refers to the process of sequence-specific post-transcriptional gene silencing in animals, mediated by short interfering RNAs (siRNAs). In another embodiment, the process of post-transcriptional gene silencing is an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes. Such protection from foreign gene expression evolved in one embodiment, in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or in another embodiment, from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA of viral genomic RNA. In one embodiment, the presence of dsRNA in cells triggers the RNAi response. In one embodiment, the siRNA used in the compositions and methods provided herein interferes with the expression of a heavy chain (V_H) of an anti-desmoglein pathogenic autoantibody, encoded by VH3-07, VH3-30, VH3-53, or any combinations thereof.

In one embodiment, the siRNA of the gene encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody described herein exhibits substantial complementarity to its target sequence. In another embodiment, "complementarity" refers to an oligonucleotide has a base sequence containing an at least 15 contiguous base region that is at least 70% complementary, or in another embodiment at least 75% complementary, or in another embodiment at least 80% complementary, or in another embodiment at least 85% complementary, or in another embodiment at least 90% complementary, or in another embodiment at least 95% complementary, or in another embodiment 100% complementary to an-at least 15 contiguous base region present of a target gene sequence (excluding RNA and DNA equivalents). (Those skilled in the art will readily appreciate modifications that could be made to the hybridization assay conditions at various percentages of complementarity to permit hybridization of the oligonucleotide to the target sequence while preventing unacceptable levels of non-specific hybridization). The degree of complementarity is determined by comparing the order of nucleobases making up the two sequences and does not take into consideration other structural differences which may exist between the two sequences, provided the structural differences do not prevent hydrogen bonding with complementary bases. The degree of complementarity between two sequences

can also be expressed in terms of the number of base mismatches present in each set of at least 15 contiguous bases being compared, which may range from 0-3 base mismatches, so long as their functionality for the purpose used is not compromised.

In one embodiment oligomeric antisense compounds, particularly oligonucleotides, are used in modulating the function of nucleic acid molecules encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody, ultimately modulating the amount of the pathogenic autoantibody produced. This is accomplished by providing antisense compounds which specifically hybridize with one or more nucleic acids encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody. In one embodiment, the terms "target nucleic acid" and "nucleic acid encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody " encompass DNA encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody, RNA (including pre-mRNA and mRNA) transcribed from such DNA, and also cDNA derived from such RNA. The specific hybridization of an oligomeric compound with its target nucleic acid interferes in another embodiment, with the normal function of the nucleic acid. The modulation of function of a target nucleic acid by compounds which specifically hybridize to it, is referred to in one embodiment as "antisense". In one embodiment, the functions of DNA to be interfered with using the antisense oligonucleotides described herein, which are used in the methods and compositions described herein, include replication and transcription. In another embodiment, functions of RNA to be interfered with include all vital functions such as, for example, translocation of the RNA to the site of protein translation, translation of protein from the RNA, splicing of the RNA to yield one or more mRNA species, and catalytic activity which may be engaged in or facilitated by the RNA. The overall effect of such interference with target nucleic acid function is modulation of the expression of the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody. In one embodiment, inhibition of gene expression is preferred and mRNA is a preferred target. In one embodiment, since many genes (including VH3-07 or VH3-30, or the combinations thereof) have multiple transcripts, "inhibition" also includes an alteration in the ratio between gene products, such as alteration of mRNA splice products.

In one embodiment, specific nucleic acids are targeted for antisense. "Targeting" an antisense compound to a particular nucleic acid, in one embodiment, is a multistep process. The process usually begins with the identification of a nucleic acid sequence whose function is to be inhibited. This may be, for example, a cellular gene (or mRNA transcribed from the gene) whose expression is associated with a particular disorder

or disease state, or a nucleic acid molecule from an infectious agent. In one embodiment, the target is a nucleic acid molecule encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody. The targeting process also includes in another embodiment, determination of a site or sites within this gene for the antisense interaction to occur such that the desired effect, e.g., inhibition of expression of the protein such as an anti-desmoglein (anti-Dsg) pathogenic autoantibody, will result. In one embodiment, an intragenic site is the region encompassing the translation initiation or termination codon of the open reading frame (ORF) of the gene. Since, the translation initiation codon is in one embodiment 5'-AUG (in transcribed mRNA molecules; 5'-ATG in the corresponding DNA molecule), the translation initiation codon is referred to in one embodiment as the "AUG codon," the "start codon" or the "AUG start codon". In another embodiment, a minority of genes have a translation initiation codon having the RNA sequence 5'-GUG, 5'-UUG or 5'-CUG, and 5'-AUA, 5'-ACG and 5'-CUG and have been shown to function in vivo. Thus, the terms "translation initiation codon" and "start codon" encompasses in other embodiments, many codon sequences, even though the initiator amino acid in each instance is typically methionine (in eukaryotes) or formylmethionine (in prokaryotes). In another embodiment, "start codon" and "translation initiation codon" refer to the codon or codons that are used in vivo to initiate translation of an mRNA molecule transcribed from a gene encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody, regardless of the sequence(s) of such codons.

Antisense compounds are used in one embodiment, as research reagents and diagnostics. In another embodiment, antisense oligonucleotides, which are able to inhibit gene expression, such as the gene encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody, with extreme specificity, are used by those of ordinary skill to elucidate the function of particular genes. Antisense compounds are used in another embodiment, to distinguish between functions of various members of a biological pathway. Antisense modulation is, in one embodiment of the agents described in the methods and compositions described herein, being harnessed for research use.

In one embodiment, the specificity and sensitivity of antisense agents described herein, is also harnessed for therapeutic uses. Antisense oligonucleotides are employed in one embodiment, as therapeutic moieties in the treatment of disease states in animals and man. In one embodiment, antisense oligonucleotides are safely and effectively administered to humans. In one embodiment oligonucleotides are useful therapeutic

modalities that can be configured to be useful in treatment regimes of cells, tissues and animals, especially humans.

Treatment

The term "treatment", or "treating" refers to any process, action, application, therapy, or the like, wherein a subject, including a human being, is subjected to medical aid with the object of improving the subject's condition, directly or indirectly. The term "treating" refers also to reducing incidence, or alleviating symptoms, eliminating recurrence, preventing recurrence, preventing incidence, improving symptoms, improving prognosis or combination thereof in other embodiments.

"Treating" embraces in another embodiment, the amelioration of an existing condition. The skilled artisan would understand that treatment does not necessarily result in the complete absence or removal of symptoms. Treatment also embraces palliative effects: that is, those that reduce the likelihood of a subsequent medical condition. The alleviation of a condition that results in a more serious condition is encompassed by this term. Therefore, in one embodiment, the invention provides a method of treating PF, comprising the step of contacting a biological sample of said subject with an effective amount of an agent capable of inhibiting the expression or function of the gene encoding the variable region of an anti-desmoglein (anti-Dsg) pathogenic autoantibody, whereby the inhibition of expression or function that gene or its encoded proteins results in depleting a biological sample from an anti-desmoglein pathogenic antibody.

Accordingly and in one embodiment, provided herein is a method of depleting a biological sample from an anti-desmoglein pathogenic antibody, comprising contacting the sample with an immobile composition comprising an agent capable of binding to a variable region of an anti-desmoglein pathogenic autoantibody; and removing the biological sample without the bound variable region of the heavy chain (V_H) of an anti-desmoglein pathogenic autoantibody, thereby depleting the biological sample of anti-desmoglein (Dsg) pathogenic autoantibody. In one embodiment, depletion of the biological sample from an anti-desmoglein pathogenic antibody, is achieved using plsmapheresis.

In another embodiment, provided herein is a method of depleting a biological sample from an anti-desmoglein pathogenic antibody, comprising contacting the sample with an immobile composition comprising an anti-autoimmune reagent capable of binding to a variable region of an anti-desmoglein pathogenic autoantibody; and removing the biological sample without the bound variable region of the heavy chain (V_H) of an anti-desmoglein

pathogenic autoantibody, thereby depleting the biological sample of anti-desmoglein (Dsg) pathogenic autoantibody. In one embodiment, the heavy chain (V_H) of an anti-desmoglein pathogenic autoantibody, is encoded by VH3-07, VH3-30, VH3-53 genes, or the combinations thereof.

In one embodiment, it is desirable to deplete the biological sample from all anti-Dsg antibodies, whether pathogenic or not. Accordingly and in another embodiment, provided herein is a method of depleting a biological sample from an anti-desmoglein antibody, comprising contacting the sample with an immobile composition comprising an anti-autoimmune reagent capable of binding to a variable region of an anti-desmoglein autoantibody; and removing the biological sample without the bound variable region of the anti-desmoglein autoantibody, thereby depleting the biological sample of anti-desmoglein (Dsg) autoantibody.

In one embodiment, the anti-autoimmune reagents of the invention is useful in removing toxic or unwanted elements, for example, plasma constituents implicated in disease, such as complement or antibodies, from the blood of a patient. The term "plasmapheresis" refers to the separation of a portion of the plasma fraction of the blood from the cellular components thereof. In another embodiment, continuous plasmapheresis is used therapeutically to remove pathologic substances contained in the plasma portion of the blood, such as an anti-Dsg3 autoantibody, or an anti-Dsg_1 and anti-Dsg_3 autoantibody (Anti-$Dsg_{1,3}$ autoantibody) in certain embodiments. In another embodiment, continuous plasmapheresis is used therapeutically to separate the cellular components from the diseased plasma and returning the cellular components to the patient in admixture with a suitable replacement fluid, or in one embodiment, by further fractionating the patient's plasma to remove the unwanted substances , such as an anti-Dsg3 autoantibody, or an anti-Dsg_1 and anti-Dsg_3 autoantibody (Anti-$Dsg_{1,3}$ autoantibody) in certain embodiments and returning a major portion of the patient's plasma with the depleted cellular components.

In one embodiment, the plasmapheresis used to remove the autoimuune antibodies, is selective plasmapheresis. In another embodiment, the techniques used is selectively removing only the clinically undesirable plasma proteins while leaving the bulk of the remainder of the plasma components in the donor's circulation, thereby enabling extensive plasmapheresis without the need for any plasma replacement. In one embodiment the plasma fraction, after being separated from the corpuscular element fraction, is treated so as to remove one or more selected plasma proteins therefrom, such as a pathogenic antibody. In one embodiment, the protein-depleted plasma fraction is obtained by passing the plasma

fraction through an immunoadsorption column to cause adsorption of certain immunoglobulins and/or immune complexes. This technique provides in another embodiment, a high degree of specificity in the profile of proteins removed. In another another embodiment of a selective plasmapheresis technique utilized in conjunction with the methods and compositions provided herein, forced-flow electrophoresis is employed for separating an immunoglobulin-rich fraction from plasma on the basis of differences in electrophoretic mobility.

In one embodiment, the biological sample used in the methods described herein, is blood, sera, plasma or a combination thereof.

In one aspect, the autoantibody and/or other immunologically active elements are removed from the blood by loading an anti-autoimmune reagent that is specific to the autoantibody and/or immunologically active elements onto a solid support or otherwise immobilized on a solid substrate to allow for separation of the autoantibody. When a sample is passed through a solid substrate containing an anti-autoimmune reagent, the anti-autoimmune reagent binds to the corresponding autoantibody, thereby removing the autoantibody from the sample. For example, beads (e.g., magnetic beads) can be coated with an anti-autoimmune reagent. The beads can easily be removed by passing the cultured cells through a magnetic column. Procedures for separation may include magnetic separation, using anti-autoimmune reagent-coated magnetic beads or dynal beads, affinity chromatography, and "panning" with antibody attached to a solid matrix, e.g., plate, or other convenient technique.

Accordingly, the invention provides a method of treating autoimmune conditions of a patient comprising filtering the patient's blood or otherwise separating a plasma constituent from the blood of the present invention and returning the cellular components back to the patient. In one aspect, the method comprises removing autoantibody from the patient's blood using anti-autoimmune reagents of the present invention.

Targeting B-cells:

Autoimmune diseases are a class of diseases associated with a B-cell disorder. Examples include including immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, dermatomyositis, Sydenham's chorea, myasthenia gravis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, polyglandular syndromes, bullous pemphigoid, diabetes mellitus, Henoch-Schonlein purpura, post-streptococcal nephritis, erythema nodosum,

Takayasu's arteritis, Addison's disease, rheumatoid arthritis multiple sclerosis, sarcoidosis, ulcerative colitis, erythema multiforme, IgA nephropathy, polyarteritis nodosa, ankylosing spondylitis, Goodpasture's syndrome, thromboangitis ubiterans, Sjogren's syndrome, primary biliary cirrhosis, Hashimoto's thyroiditis, thyrotoxicosis, scleroderma, chronic active hepatitis, polymyositis/dermatomyositis, polychondritis, pamphigus vulgaris, Wegener's granulomatosis, membranous nephropathy, amyotrophic lateral sclerosis, tabes dorsalis, giant cell arteritis/polymyalgia, pernicious anemia, rapidly progressive glomerulonephritis and fibrosing alveolitis. The most common treatments are corticosteroids and cytotoxic drugs, which can be very toxic. These drugs also suppress the entire immune system which can result in serious infection have adverse affects on the liver and kidneys. The present invention provides a method of targeting B cells using an anti-autoimmune reagent that is capable of binding to an autoantibody.

B-cell clones that bear autoantibody Ig-receptors are present in normal individuals. Autoimmunity results when these B-cells become overactive, and mature to plasma cells that secrete autoantibody. In accordance with the present invention, autoimmune disorders can be treated by administering an anti-autoimmune reagent (e.g., an antibody or polypeptide) that binds to an autoantibody present on a B-cell, such as an anti-desmoglein antibody. In one embodiment, the anti-autoimmune reagent is conjugated with to a therapeutic moiety including, but not limited to an anti-tumor agent, a chemotherapeutic agent, an anti-cell proliferation agent, a drug, a toxin, a therapeutic radioisotope, and any combination thereof.

The present invention contemplates the use of anti-autoimmune reagents for treatment of autoimmune diseases. For example, preferred anti-autoimmune reagents are antibodies or polypeptides that bind to an anti-desmoglein antibody or fragment thereof such as an anti-desmoglein antibody comprising an amino acid sequence represented by SEQ ID NOs: 44-86, 173-215, 216-258 or any combination thereof. Prefereably, the anti-desmoglein antibody is pathgenic and is encoded by VH3-07, VH3-30, VH3-53 genes, or the combinations thereof. In a preferred embodiment, the anti-autoimmune reagents are conjugated or fused to a therapeutic moiety. In some instances, the anti-autoimmune reagent is used to deplete the blood or a biological sample of B-cells that express on their surface anti-desmoglein antibodies.

The anti-autoimmune reagents of the invention can be used in combination with other exisitng therapies in the art. For example, the anti-autoimmune reagents can be administered to mammal, preferably a human, before, concurrently or after administration of

other types of therapy. For example, the anti-autoimmune reagent can be co-administered with therapeutics that target against T-cells, plasma cells or macrophages, such as antibodies directed against T-cell epitopes, more particularly against the CD4 epitopes. Gamma globulins also may be co-administered. In some cases, it may be desirable to co-administer immunosupproessive drugs such as corticosteroids and possibly also cytotoxic drugs. In this case, lower doses of the corticosteroids and cytotoxic drugs can be used as compared to the doses used in conventional therapies, thereby reducing the negative side effects of these therapeutics.

Drugs which are known to act on B-cells, plasma cells and/or T-cells are particularly useful in accordance with the present invention, whether conjugated to an anti-autoimmune reagent, or administered as a separate component in combination with the anti-autoimmune reagent. These include methotrexate, phenyl butyrate, bryostatin, cyclophosphamide, etoposide, bleomycin, doxorubicin, carmustine, vincristine, procarbazine, dexamethasone, leucovorin, prednisone, maytansinoids such as DM1, calicheamicin, rapamycin, leflunomide, FK506, immuran, fludarabine, azathiopine, mycophenolate, and cyclosporin. Drugs such as immuran, methotrexate, and fludarabine which act on both B-cells and T-cells are particularly preferred. Illustrative of toxins which are suitably employed in accordance with the present invention are ricin, abrin, ribonuclease, DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtheria toxin, Pseudomonas exotoxin, Pseudomonas endotoxin and RNAses, such as onconase. Other suitable drugs and toxins are known to those of skill in the art.

Cytokine agonists and antagonists may also be used in the therapies according to the present invention. Tumor necrosis factor alpha (TNFα) and interleukin-1 (IL-1) are important in mediating inflammation in rheumatoid arthritis. Accordingly, anti-TNFα reagents, such as infliximab and etanercept (Enbrel), are useful in therapy according to the invention, as well as anti-IL-1 reagents. Other useful secondary therapeutics included IL-2 and GM-CSF, which may be conjugated with the anti-autoimmune reagent.

Diagnostic Tools:

In one embodiment, provided herein is a method of diagnosing pemphigus in a subject, comprising the step of contacting a biological sample of said subject with a composition comprising an anti-autoimmune reagent described herein, for example an antibody that specifically binds to an anti-desmoglein (Dsg) pathogenic autoantibody; and

analyzing the biological sample for the presence of antibody-antigen complex, whereby the presence of antibody-antigen complex indicates the subject has or is predisposed to pemphigus.

In another embodiment, the step of contacting a biological sample of said subject with a composition comprising the anti-idiotypic antibody described herein, is affected using a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, or a combination thereof.

In one embodiment, when using RIA, a labeled anti-idiopathic antibody as described herein is contacted with a sample containing an unknown amount of substrate in varying amounts. The decrease in precipitated counts from the labeled anti-idiotypic antibody is proportional to the amount of anti-Dsg antibodies in the added sample, indicating pemphigus.

In another embodiment, when using ELISA, the anti-idiotypic antibody provided herein, which is coupled to an enzyme is applied and allowed to bind to react with the sample. Presence of the anti-Dsg antibody is then detected and quantitated by a colorimetric reaction employing the enzyme coupled to the anti-idiotypic antibody. In another embodiment, enzymes employed in this method are horseradish peroxidase or in another embodiment alkaline phosphatase. In the dynamic range of response, the amount of anti-Dsg antibodies present in the sample is proportional to the amount of color produced. A substrate standard is employed in one embodiment, to improve quantitative accuracy.

The use of the anti-autoimmune reagents of the present invention are more sensitive in the context of a diagnostic test for pathology of pemphigus because the anti-autoimmune reagents are able to specifically bind to pathogenic antibodies. Prior to the present invention, the diagnostic tests for pemphigus would sometimes result in false positive identification of pemphigus patients because the reagents used by the prior art would sometimes recognized non-pathogenic antibodies.

Administration

In some embodiments, an effective amount of the compositions of the present invention (e.g., anti-idiotypic antibody or otherwise inhibitors of pathogenic PF antibodies) is administered to a mammal, preferably a mammal. In other embodiments, a therapeutically effective amount of the compositions of the present invention are administered to a mammal, preferably a human, for the treatment of a disease or condition.

The term "effective amount" as used herein is defined as the amount of the compositions of the present invention that is necessary to result in a physiological change in the cell or tissue to which it is administered.

The term "therapeutically effective amount" as used herein is defined as the amount of the compositions of the present invention that eliminates, decreases, delays, or minimizes adverse effects of a disease, such as pemphigus. A skilled artisan readily recognizes that in many cases the compositions may not provide a cure but may only provide partial benefit, such as alleviation or improvement of at least one symptom of the disease.

Pharmaceutical compositions comprising the compositions of the invention may be manufactured by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Pharmaceutical compositions may be formulated in conventional manner using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries that facilitate processing of the proteins into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For topical administration the proteins of the invention may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art.

Systemic formulations include those designed for administration by injection, e.g. subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal, inhalation, oral or pulmonary administration.

For injection, the compostions of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. The solution may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the proteins may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the proteins can be readily formulated by combining the proteins with pharmaceutically acceptable carriers well known in the art. Such carriers enable the proteins of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. For oral solid formulations such as, for example, powders, capsules and tablets,

suitable excipients include fillers such as sugars, e.g. lactose, sucrose, mannitol and sorbitol; cellulose preparations such as maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP); granulating agents; and binding agents. If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

If desired, solid dosage forms may be sugar-coated or enteric-coated using standard techniques.

Alternatively, other pharmaceutical delivery systems may be employed. Liposomes and emulsions are well-known examples of delivery vehicles that may be used to deliver proteins of the invention. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the molecules may be delivered using a sustained-release system, such as semipermeable matrices of solid polymers containing the therapeutic agent. Various of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the molecules for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the chimeric molecules, additional strategies for molecule stabilization may be employed.

The compositions of the invention may contain charged side chains or termini. Thus, they may be included in any of the above-described formulations as the free acids or bases or as pharmaceutically acceptable salts. Pharmaceutically acceptable salts are those salts that substantially retain the biologic activity of the free bases and which are prepared by reaction with inorganic acids. Pharmaceutical salts tend to be more soluble in aqueous and other protic solvents than are the corresponding free base forms.

The compostions of the invention will generally be used in an amount effective to achieve the intended purpose. For use to treat or prevent a disease condition, the molecules of the invention, or pharmaceutical compositions thereof, are administered or applied in a therapeutically effective amount.

For systemic administration, a therapeutically effective dose can be estimated initially from in vitro assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture. Such information can be used to more accurately determine useful doses in humans.

Initial dosages can also be estimated from in vivo data, e.g., animal models, using techniques that are well known in the art. One having ordinary skill in the art could readily optimize administration to humans based on animal data.

Dosage amount and interval may be adjusted individually to provide plasma levels of the molecules which are sufficient to maintain therapeutic effect. Usual patient dosages for administration by injection range from about 0.001 to 100 mg/kg/day, preferably from about 0.5 to 1 mg/kg/day and any and all whole or partial integers there between. Therapeutically effective serum levels may be achieved by administering multiple doses each day.

In cases of local administration or selective uptake, the effective local concentration of the proteins may not be related to plasma concentration. One having skill in the art will be able to optimize therapeutically effective local dosages without undue experimentation.

The amount of the compositions of the present invention administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

The therapy may be repeated intermittently while symptoms detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs.

The following examples are presented in order to more fully illustrate the preferred embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

EXAMPLES

Materials and Methods:

Construction of Phage Library

Separated IgG-λ and IgG-κ phage libraries were constructed from 1 x 10^7 mononuclear cells isolated from 50 ml of peripheral blood collected from a PF patient with clinically active disease (Barbas,C.F., III, Burton,D.R., Scott,J.K., and Silverman,G.J. 2001. Phage display: a laboraroty manual. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA). Briefly, RT-PCR was used to amplify the immunoglobulin variable regions of the heavy (VH) and light chains (VL), and the gene fragments were then cloned into the phagemid vector pComb3X (Scripps Institute, La Jolla, CA). The phagemid library was electropolated into XL-1 Blue suppressor strain of E. coli (Stratagene) with

superinfection by VCSM13 helper phage (Stratagene). In this system, filamentous phage particles express scFv antibodies (with a carboxy-terminal 6x histidine tag and a hemagglutinin [HA] tag) fused to the pIII bacteriophage coat protein. Recombinant phage were purified from culture supernatants by polyethylene glycol precipitation and resuspended in PBS, pH 7.4 with 1% BSA containing1 mM $CaCl_2$. The library comprised more than 2 x 10^8 independent transformants as determined by titering on *E. coli* XL1-Blue after transformation. To validate library diversity, the sequences of 14 phage clones from the unpanned library were analyzed. No duplicate sequences and marked heterogeneity in VH and VL gene usage were found, similar to that found in normal human peripheral blood lymphocytes.

Phage selection against Dsg1 absorbed to a solid phase

ELISA plates coated with recombinant Dsg1 (MBL) were used to isolate phage clones that express anti-Dsg1 scFv as previously described (Payne et al., 2005 J.Clin.Invest 115:888-899.). Briefly, four wells were incubated with blocking buffer (50 mM Tris pH 7.5, 150mM NaCl, 1mM CaCl2[TBS-Ca] with 3% skim milk) at room temperature for 1 hour. The phage library was diluted into blocking buffer and was incubated with Dsg1 on the wells for 2 hours at room temperature. After 5 to 10 washes with TBS-Ca containing 0.1% Tween 20, adherent phage were eluted with 76 mM citric acid, pH 2.4, incubated for 10 minutes at room temperature, and then neutralized with 2M unbuffered Tris. The eluted phage were amplified in XL1-Blue *E. coli* and rescued by superinfection with VCSM13 helper phage. Phage were harvested from bacterial culture supernatant and then re-panned against Dsg1 ELISA plates for three additional rounds. Individual phage clones were isolated from each round of panning and analyzed for the binding to Dsg1 by ELISA using horseradish peroxidase (HRP)-conjugated anti-M13 antibody (GE Healthcare Bio-Sciences). For epitope-blocked panning, the phage library was first mixed with purified recombinant non-pathogenic scFvs (clones 1-18/L1, 1-18/L12, 3-094/O18O8, and 3-093/O12O2) and then incubated on immobilized Dsg1 for 2 hours at room temperature.

Phage selection against mammalian produced Dsg1 in solution

cDNA encoding the extracellular region of human Dsg1 fused with the Fc portion of human IgG1 and a histidine tag (6 histidine residues) (Dsg1-IgHis) was subcloned into pcDNA3-1 (Invitrogen). The resultant construct was transiently transfected into 293T cells using jet PEI (Polyplus-transfection Inc.). The recombinant protein was purified from

the culture supernatant with Talon metal affinity resin according to manufacturer's protocol (Clontech Laboratories, Inc.)

The PF patient antibody phage library (2 X 10^{11} colony forming units) was precleared by incubation with the Fc fragment of human IgG (Jackson ImmunoResearch Laboratories, Inc.) which was then removed by protein G magnetic beads (New England Biolabs). The precleared phage library was then incubated with recombinant Dsg1-IgHis at room temperature for 20 min. Phage bound to Dsg1-IgHis were captured by protein G magnetic beads, washed with TBS containing 0.1 % Tween 20, then eluted with 0.2 M glycine-HCl, pH 2.2 and immediately neutralized with 1M Tris-HCl, pH 9.1. Eluted phage were amplified in XL1-Blue *E. coli* followed by superinfection with helper phage as described above. Phage were harvested from bacterial culture supernatant and re-panned against Dsg1-IgHis in solution. Protein G magnetic beads and Protein A magnetic beads (New England Biolabs) were used in alternate rounds of panning to avoid isolation of phage that bound non-specifically to Protein A or G.

Sequence analysis of scFv antibodies

Recombinant phagemids were purified with a plasmid preparation system (Qiagen) and the VH and VL inserts were sequenced using pComb3X specific primers previously described (Barbas,C.F., III, Burton,D.R., Scott,J.K., and Silverman,G.J. 2001. Phage display: a laboraroty manual. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA). The nucleotide sequences were compared with the germline sequences in V Base sequence directory (http://vbase.mrc-cpe.cam.ac.uk/) to determine their germline gene origins and interrelatedness.

Production and purification of soluble scFvs

The Top10 F' non -suppressor strain of E. coli (Invitrogen Corp.) was infected with an individual phage clone and soluble scFvs were purified from the bacterial periplasmic space using sucrose shock or Fastbeak (Promega) and Talon metal affinity resin (Clontech Laborarories, Inc.) as previously described (Payne et al., 2005 J.Clin.Invest 115:888-899).

Dsg1 and Dsg3 scFv ELISA

The reactivity of scFv against human Dsg1 and Dsg3 was measured by Dsg1 and Dsg3 ELISA (MBL) using HRP-conjugated anti-HA monoclonal antibody (clone

12CA5, 1:1000 dilution, Roche Diagnostics Corp.) as a secondary antibody as described is Payne et al., 2005 J.Clin.Invest 115:888-899.

Inhibition of scFv binding by pemphigus sera

Inhibition ELISA to block the binding of scFv to Dsg1 by pemphigus sera was performed as previously (Payne et al., 2005 J.Clin.Invest 115:888-899). Briefly, scFvs were used at dilutions that resulted in an OD450 reading of approximately 1.0 in the Dsg1 ELISA in the absence of blocking serum. The diluted scFv, mixed with pemphigus or normal control sera (10 uL), was analyzed by Dsg1 ELISA developed with HRP- conjugate anti-HA antibody. Inhibition was calculated according to the following formula: % inhibition = [1-(OD S/B-OD Sc/B)/(OD S/Bc - OD Sc/Bc)] x 100 where S is the scFv being tested, Sc is scFv negative control, B is blocking pemphigus serum and Bc is normal human serum.

Inhibition of PF sera binding by scFvs

PF sera were diluted to result in an OD 450 reading of approximately 1.0 in the Dsg1 ELISA without competitors. The diluted PF sera, mixed with scFvs, were analyzed by Dsg1 ELISA developed with HRP-conjugate anti- human Fab antibody. Inhibition was calculated according to the following formula: % inhibition = [1-(OD T/B-OD N/B)/(OD T/Bc-OD N/Bc)] x 100 where T is the PF sera tested, N is normal control serum, B is blocking monoclonal anti-Dsg1 scFvs, Bc is control scFv (AM3-13).

Epitope mapping by competition ELISA

Extracellular, domain-swapped desmoglein 1 and 3 recombinant molecules were produced by a baculovirus expression system as previously described (Futei et al., 2000 J.Invest Dermatol. 115:829-834.). ScFvs were diluted so that Dsg1 ELISA readings at OD450 were approximately 1.0 in the absence of a competitor. The diluted scFvs were incubated with an excess amount of baculovirus culture supernatant containing the recombinant proteins for 30 minutes at room temperature. Immunoblot analysis confirmed that each culture supernatant contained approximately the same amount of recombinant protein. The mixture was subjected to Dsg1 ELISA (MBL) developed with HRP-anti-HA antibody. Inhibition was calculated using the following formula: Inhibition (%) = [1 – (OD competitor – OD blank)/(OD negative – OD blank)] x 100; OD competitor is an OD obtained with scFv incubated with culture supernatant with a recombinant baculoprotein; OD negative is an OD obtained with sera incubated with culture supernatant of uninfected High

Five insect cells; OD blank is an OD obtained with secondary antibody only. Greater than 40 % inhibition was considered positive.

Direct and indirect immunofluorescence

Immunofluorescence for scFvs was performed on human skin, mouse tail or neonatal mouse skin as previously described (Payne et al., 2005 J.Clin.Invest 115:888-899). Binding was detected with rat monoclonal anti-HA antibody (3F10, 1:100 dilution, Roche Diagnostics) followed by Alexa Fluor 568-conjugated anti-rat IgG (1:200 dilution, Invitrogen).

Immunoblotting

The ectodomain of human Dsg1 tagged with an E-tag and a histidine tag (Dsg1-EHis), produced by a baculovirus expression system was used as substrate (Ishii et al., 1997 J.Immunol. 159:2010-2017.). The recombinant proteins were size fractionated by SDS-PAGE and transferred to nitrocellulose membranes. The membranes were incubated with scFvs diluted in PBS/ 5% milk following by HRP-conjugated anti-HA antibody (1:1000 dilution; Roche Diagnostics) and developed by ECL plus reagent (GE Healthcare Bio-Sciences).

Immunoprecipitation-immunoblotting analysis for Dsg4 binding

To determine whether anti-Dsg1 scFvs also bind Dsg4, baculovirus-produced recombinant human Dsg4-EHis and human Dsg1-EHis ("EHis" tag defined above) was used (Nagasaka et al., 2004 J.Clin.Invest 114:1484-1492.). Baculovirus-infected insect cell culture supernatants containing recombinant molecules were incubated with scFvs for 30 minutes and then immunoprecipitated with anti-HA agarose (Sigma -Aldrich) at 4°C for 2 hours with gentle rotation. After washing with TBS-Ca, the immunoprecipitates were resuspended in Laemmli sample buffer, separated by SDS-PAGE, and transferred to nitrocellulose membranes (Bio-Rad Labratories). Membranes were probed with HRP-conjugated anti-E-tag antibody (1:2000 dilution, GE Healthcare Bio-Sciences).

Neonatal mouse injection

Purified scFv (100 uL) were injected subcutaneously along the back into 1-2 day old neonatal C57Bl/6J mice. The mice were sacrificed at 6 hours and skin was harvested for direct immunofluorescene and for histology.

Human skin organ culture injection

Specimens were obtained from left over normal skin after excisional surgery. The specimens were trimmed by removing fat tissue and cut into 5 mm diameter pieces. After intradermal injection of 50 uL of purified scFv using an insulin syringe, skin specimens were put on the insert of transwells (Corning) with defined keratinocyte SFM (Invitrogen) containing 1.2 mM CaCl2 in the outer compartment. At 24 hours, the skin was harvested for direct immunofluorescene and for histology.

Example 1: Immunochemical properties of the anti-Dsg1 scFv are associated with their heavy-chain gene usage

ELISA analysis

Representative soluble scFvs were tested for binding to Dsg1 (Figure 1) and Dsg 3 by ELISA. All scFvs bound Dsg1 as expected, and did not bind Dsg3, except for two 3-07/1e clones (differed from each other only in their light chain VJ recombination) that showed weak binding to Dsg3 at very high concentrations (data not shown). Six VH1-18 clones bound strongly by ELISA, giving an OD450 = 1 values at concentrations from 0.4 to 2.8 ng/ml (2 clones shown in Figure 1, light green lines). VH3-09 clones also showed good binding; 9 of 12 clones tested gave OD450 = 1 values at 0.5-20 ng/ml (i.e. dark green lines in Figure 1). The VH1-08 and VH3-07 clones showed much weaker binding, and the VH3-30 clone showed intermediate binding (Figure 1).

Indirect immunofluorescence on mouse tail and human skin

All VH1-18 clones stained the cell surface of keratinocytes throughout human epidermis, stronger in the more superficial epidermis, identical to staining reported with PF serum (Table 1). This pattern was also seen when antibodies were injected into human skin organ culture (Figure 5B). These VH1-18 antibodies did not stain mouse skin. In contrast, VH3-09 antibodies stained the cell surface of human keratinocytes weakly, if at all, and also did not bind mouse skin. There was a suggestion of some cytoplasmic staining of human epidermis with some of these VH3-09 antibodies, most marked with 3-094/O18O8 (Figure 2). The VH3-07 and VH3-30 clones strongly stained the cell surface of both human and mouse epidermis (3-30/3h shown in Figure 2, also see Figure 5). The staining with 3-30/3h was eliminated when the human skin was preincubated with EDTA (Figure 2), suggesting that the antibody binds a calcium-sensitive epitope.

Table 1: Anti-Dsg1 clones representing each unique heavy chain (VDJ) and their associated light chain genes

VH gene		Unique VDJ region[a]	D gene	J gene	VL gene	Name of clone	IIF		Dsg1 IB	Dsg4 binding	Patho-genicity	Dsg1 epitope
							Human skin	Mouse skin				
VH1	VH1-18	VDJ1	D3-10/DXP'1	JH4b	B3	1-18/B3	+		+			
					L8	1-18/L8	+	—	+			
					L1	1-18/L1	+	—	+	—	—[b]	164-401
					L12	1-18/L12	+	weak +	+	—	—	164-401
					L2	1-18/L2						
					LFVK431	1-18/LFVK431	+		+			
	VH1-08	VDJ2	D3-3/DXP4	JH6b	O12/O2	1-08/O12O2	+	+	—	+	—	1-161
VH3	VH3-09	VDJ3	D2-2	JH6b	O12/O2	3-09[3]/O12O2	weak+[c]	weak+	—		—	
					O18/O8	3-09[3]/O18O8			—			
					L11	3-09[3]/L11						
					A30	3-09[3]/A30						
					1c	3-09[3]/1c						
					1e	3-09[3]/1e						
					1g	3-09[3]/1g						
					6a	3-09[3]/6a						
		VDJ4	D3-3/DXP4	JH3a	O18/O8	3-09[4]/O18O8	—[d]	weak+	—	+	—	1-161
		VDJ5			O18/O8	3-09[5]/O18O8	+	+	—		—	1-161
					L11	3-09[5]/L11						
		VDJ6			L12	3-09[6]/L12	—					
					O18/O8	3-09[6]/O18O8	weak +					
					1c	3-09[6]/1c						
		VDJ7	D3-3/DXP4	JH3b	O12/O2	3-09[7]/O12O2	—					
					1c	3-09[7]/1c	weak +	weak +	—	+	—	1-161
		VDJ8	D3-22/D21-9	JH4b	L11	3-09[8]/L11	weak +		—			
		VDJ9	D2-8/DLR1	JH2	L8	3-09[9]/L8						
					L2	3-09[9]/L2						
		VDJ10	D1-14/DM2	JH6b	O18/O8	3-09[10]/O18O8						
	VH3-07	VDJ11	D3-10/DXP'1	JH4b	1e	3-07/1e	+	+	—	—	weak+[e]	1-161
	VH3-30	VDJ12	D5-24	JH4b	3h	3-30/3h	+	+	—	—	+	1-161

[a]Each VDJ recombinatory region is defined by a CDR3 (the third complimentarydetermining region) amino acide sequence. Because of extensive diversity in VDJ gene rearrengements, clones sharing identical VDJ sequences are considered to have arisen from the same B-cell clones.

[b]Intradermal injection into human foreskin grafted SCID mice (ref. 16) was used to test pathogenicity for this clone.

[c]one clone with unique light chain VJ junction also stained epidermal basement membrane.

[d]showed cytoplasmic staining.

[e]one clone with unique 1e VJ junction was negative.

Table abbreviations: IIF, indirect immunofluorescence; IB, immunoblot; Dsg1 epitope defined as amino acid numbers in Dsg1.

Binding to denatured Dsg1 and to unprocessed Dsg1 proprotein

VH1-18 clones bound denatured Dsg1 on immunoblots unlike any of the other clones tested (Table 1 and Figure 3A). In immunoprecipitation experiments using recombinant human Dsg1 produced by baculovirus expression system clones 3-09[4]/O18O8 and 3-09[7]/1c immunoprecipitated a Dsg1 polypeptide with a slightly greater apparent molecular weight on SDS PAGE than other clones (Figure 3B). As it is known that the insect cells transfected with the recombinant baculovirus produce both the proprotein and mature protein forms of Dsg1, this finding suggests that they bind to the proprotein but not

the mature protein. Binding to the proprotein was consistent with the cytoplasmic staining seen by indirect immunofluourescence (Figure 2), because the proprotein is believed to be processed to the mature form as it reaches the cell surface.

Binding of Dsg4

Some pemphigus sera bind Dsg4, and this binding was due to antibodies against Dsg1 that cross react with Dsg4. To determine whether any of the anti-Dsg1 monoclonal antibodies crossreact with Dsg4, scFvs were used to immunoprecipitate recombinant Dsg4 containing a carboxy-terminal E-epitope tag , then identified its presence on an immunoblot stained with anti-E tag antibodies. VH1-18, VH3-07 and VH3-30 antibodies did not bind Dsg4, whereas VH1-08 and VH3-09 antibodies did (Table 1 and Figure 3B).

Epitope mapping of anti-Dsg1 antibodies

Four Dsg1/Dsg3 chimeric molecules were used to perform competition assays with various anti-Dsg1 scFvs. As shown in Figure 4, VH1-18 clones bound to amino acids #164-401, whereas all others mapped to the amino terminus of Dsg1 (amino acids #1-161) (Table 1).

The data presented herein demonstrate, in general, that the properties of the isolated antibodies correlate with heavy chain gene usage, even if the light chains are encoded by a diversity of variable region genes. Overall, the heavy chains of our anti-Dsg1 clones were encoded by only 5 different heavy chain genes belonging to only two heavy chain gene families (VH1 and VH3), whereas light chain gene usage was siginficantly more promiscuous.

Example 2: Light chain suffling shows that only certain light chains can pair with the restricted heavy chains to allow Dsg1 binding

Although the heavy chain gene usage is generally associated with the immunochemical properties of these scFvs, and the light chain gene usage is much less restricted, light chain shuffling experiments showed that the pairing of light and heavy chains is not entirely random, as only certain light chains allow binding to Dsg1. To demonstrate the light chain contribution to Dsg1 binding, a derivative phage display library was constructed using the heavy chain of scFv 3-098/L11 paired with the entire original light chain repertoire from the PF patient. Analysis of 16 clones from this derivative library

before panning showed that none bound to Dsg1 by ELISA, even though all had the VH3-09 heavy chain. The clones did, however, bind an anti-hemagglutinin (HA) tag-coated ELISA plate, showing that the scFv (which is engineered to express the HA tag on its carboxy-terminus) was expressed on the phage surfaces. On the other hand, when this library was panned against Dsg1 to select anti-Dsg1 clones, these clones used the L11, A30 or 1c light chain genes, as were found in the anti-Dsg1 clones isolated from the original libraries. These data suggest that only certain light chains permit Dsg1 binding when paired to this heavy chain.

Example 3: Monovalent, monoclonal anti-Dsg1 ScFv can cause the pathology of PF

Initially pathogenicity was tested in the neonatal mouse model of pemphigus. Because VH1-18 and VH3-09 clones did not bind well to mouse skin by indirect immunofluorescence, it was believed seemed that theses antibodies would not bind epidermis or induce pathology, which turned out to be the case (Table 1). However, clones 1-08/O12O2 and 3-07/1e did not induce pathology either, even though they did bind mouse epidermis (Table 2, Figure 5A). Clone 3-30/3h, on the other hand, caused extensive gross blisters with the typical histology and direct immunofluorescence of PF (Figure 5A).

Table 2: Code table for PF1-scFv clones

VH gene		Common VDJ	D segment	J segment	VL gene	Original name of clones	name in paper
VH1	VH1-18	VDJ1	D3-10/DXP'1	JH4b	B3	PF1-2-7	1-18/B3
					L8	PF1-2-1	1-18/L8
					L1	PF1-2-5	1-18/L1
					L12	PF1-2-6	1-18/L12
					[redacted]	PF1-3-K11	1-18/L2
					LFVK431	PF1-2-15	1-18/LFVK431
	VH1-08	VDJ2	D3-3/DXP4	JH6b	O12/O2	PF1-2-22	1-08/O12O2
VH3	[redacted]	VDJ3	D2-2	JH6b	O12/O2	PF1-2-11.	3-09[3]/O12O2
					O18/O8	PF1-2-17	3-09[3]/O18O8
					L11	PF1-29	3-09[3]/L11
					A30	PF1-1-35	3-09[3]/A30
					1c	PF1-2-L19	3-09[3]/1c
					1e	PF1-2-L32	3-09[3]/1e
					1g	PF1-2-L4	3-09[3]/1g
					6a	PF1-2-L10	3-09[3]/6a
		VDJ4	D3-3/DXP4	JH3a	O18/O8	PF1-2-10	3-09[4]/O18O8
		VDJ5			O18/O8	PF1-2-9	3-09[5]/O18O8
					L11	PF1-3-K6	3-09[5]/L11
		VDJ6			L12	PF1-26	3-09[6]/L12
					O18/O8	PF1-22	3-09[6]/O18O8
					1c	PF1-2-L02	3-09[6]/1c
		VDJ7	D3-3/DXP4	JH3b	O12/O2	PF1-1-1	3-09[7]/O12O2
					1c	PF1-2-3	3-09[7]/1c
		VDJ8	D3-22/D21-9	JH4b	L11	PF1-2-18	3-09[8]/L11
		VDJ9	D2-8/DLR1	JH2	L8	PF1-1-7	3-09[9]/L8
					[redacted]	PF1-1-19	3-09[9]/L2
		VDJ10	D1-14/DM2	JH6b	O18/O8	PF1-27	3-09[10]/O18O8
	VH3-7	VDJ11	D3-10/DXP'1	JH4b	1e	PF1-8-2	3-07/1e
					1e	PF1-8-5	
	VH3-30	VDJ12	D5-24	JH4b	3h	PF1-8-15	3-30/3h

Given the possibility that some monoclonal anti-Dsg1 antibodies might be specific for human rather than mouse pathogenic epitopes, representative scFv clones were tested by injecting them into freshly isolated human skin biopsies, which were then maintained in organ culture for 24 hours. Immunofluorescence of these cultures showed binding of antibodies to the epidermal cell surface (except for VH3-09 antibodies, consistent with their weak binding to the keratinocyte cytoplasm by indirect immunofluorescence), but only 3-30/3h caused extensive histologic blisters with features typical of PF, while 3-07/1e caused focal blisters with typical histology (Figure 5B).

These findings demonstrate that a monovalent, anti-Dsg1monoclonal antibody that does not bind to Dsg4 can cause the pathology of PF. In addition, one clone (3-07/1e) was specific for a human pathogenic epitope, not shared in the mouse, but one clone (3-30/3h) caused disease in both humans and mice.

Example 4: A common pathologic epitope on Dsg1, defined by scFv 3-30/3H, is targeted by multiple PF sera and PV sera that contain anti-Dsg1 antibodies.

ELISA inhibition studies in which patients' sera was used to inhibit the binding of scFv to Dsg1 were used to determine if antibodies from various patients bind at or near the epitopes bound by the scFv (Table 2). Most strikingly, clone 3-30/3h, the most pathogenic scFv, was inhibited by 6/6 PF sera and 5/5 PV sera that contain both anti-Dsg3 and anti-Dsg1 antibodies, but none of 3 PV sera that contain only anti-Dsg3 antibodies (Figure 6A). It is known that in mucocutaneous PV the anti-Dsg1 antibodies are pathogenic. These results suggest that the pathogenic anti-Dsg1 antibodies in PF and mucocutaneous PV sera inhibit identical or similar epitopes to those defined by scFv 3-30/3h, suggesting that this clone defines an important epitope on Dsg1 that is targeted to cause pathology in many, if not all, PF and mucocutaneous PV patients.

Other anti-Dsg1 clones were inhibited in their binding to Dsg1 by fewer PF and PV patients' sera, suggesting that the epitopes defined by these clones were not as well preserved among patients as was that defined by clone 3-30/3h.

Characterization of the libraries also demonstrate the presence and absence of consensus CDR3 sequences in pathogenic antibodies, respectively. It was observed that a consensus sequence was present by all of the tested pathogenic antibody sequences. However, this sequence was not found in the tested nonpathogenic antibody sequences. The consensus sequence shared among the pathogenic antibodies reside in the CDR3 region of the antibody. The consensus sequence shared among the pathogenic antibodies is D/E-X-X-X-W, wherein X can represent any amino acid. The consensus sequence contains a tryptophan. A conserved tryptophan has been observed in other molecules for example cadherin. Without wishing to be bound by any particular theory, it is believed that cadherin homophilic interaction is dependent on conserved tryptophan residues in the amino terminal binding pocket. Therefore, it is believed that the tryptophan in the CDR3 region plays a role in the antigen-binding characterisitic of the antibody to desmogleins and how the pathogenic antibodies cause a disease state.

Example 5: Epitopes defined by scFvs isolated from a PF patient comprise major targets of the autoantibody respose in other PF patients

A mixture of non-pathogenic and pathogenic scFvs derived from PF patient 1 was tested for its ability to block the binding of various PF patient sera to Dsg1. As shown in

Figure 6B, the mixture blocks >90% of Dsg1 binding by the serum from the patient from whom the antibody phage display library was constructed (PF1-lib). This suggests that the isolated scFvs identify nearly all epitopes targeted by serum IgG from PF patient 1. In addition, this combination of scFvs blocks 70-100% of Dsg 1 binding in four other randomly-selected PF patient sera.

Furthermore, significant antibody responses against pathogenic epitopes are found across patients as evidenced by the ability for the two pathogenic scFv clones, 3-30/3h and 3-07/1e, to identify major pathogenic epitopes to which antibodies in many other PF sera bind closely. These two scFvs alone block 60% of binding of the serum from PF patient 1; 3-30/3h alone, the most pathogenic antibody, blocks this serum binding by almost 50%. The combination of 3-30/3h and 3-07/1e block the binding of unrelated PF patients' sera by 46-83%, showing that the epitopes defined by these 2 scFvs are likely involved in many PF patients, and antibodies that bind to them (or nearby) are a major part of the autoantibody response in PF sera.

Example 6: Enzyme-linked immunosorbaant assay (ELISA) analysis of phage clones and their scFv.

E. coli were infected with various clones isolated from the unpanned and panned PV(1) library, and the antibody-expressing phage were used directly for ELISA on Dsg1 and Dsg3. These assays were developed with horseradish peroxidase (HRP) conjugated anti-M13 (i.e. anti-phage antibody). Alternatively, plasmid DNA, derived from phage clones, was expressed in non-suppressor stains of *E. coli* to produce soluble scFv fragments, unlinked to phage. ScFv is essentially the soluble heavy and light chain variable regions (VH and VL), folded into an active antibody binding site, with a 6xHis and a hemagglutinin (HA) tag on its carboxy-terminus for purification and detection purposes, respectively. ScFv were used for ELISA on Dsg1 and Dsg3, and detected with HRP-conjugated rat anti-HA tag. Irrelevant phage or scFv were used as controls. Phage panned on Dsg3 (or its scFv) showed positive Dsg3 binding on ELISA. Interestingly, one phage clone, D(3)4-3 showed slight binding to Dsg1. Phage or scFv derived from Dsg3/Dsg1 alternating panning scheme showed binding to both desmogleins by ELISA (Figure 7).

Example 7: Use of a human monoclonal autoantibody to identify pathogeneic epitopes by peptide phage display

Pathogenic PF anti-Dsg mAbs are used as targets for the panning of peptide

display libraries to isolate peptides that mimic Dsg epitopes and block the binding of anti-Dsg antibodies. To demonstrate the feasibility of this approach, the results of an analogous experiment performed with an autoantibody, H44L4 are presented, isolated from an antibody phage display library derived from an ITP patient. H44L4, a human anti-integrin $\alpha_{2b}\beta_3$ platelet function-inhibiting mAb, was incubated with two commercially-available peptide phage display libraries – a 12-mer linear peptide library and a 7-mer constrained (i.e. cysteines on each end) peptide library. After several rounds of panning, peptides were isolated from both libraries that not only bound to their target (H44L4), but inhibited the binding of the anti-$\alpha_{2b}\beta_3$autoantibody to $\alpha_{2b}\beta_3$ as assessed by ELISA and flow cytometry with intact platelets. In the case of ITP, these results demonstrate our ability to isolate peptides (using peptide phage display) that block the binding of a human autoantibody (originally derived using antibody phage display) to its autoantigen. Furthermore, these data show that such peptides can mimic conformational epitopes, i.e. epitopes comprising amino acid residues juxtaposed next to each other due to protein folding (Figure 8).

Peptide phage display and techniques

PhD-12 and PhD-C7C peptide phage display libraries (New England BioLabs) is screened with PF IgG according to manufacturer's instructions, alternating between protein A and protein G magnetic beads (New England BioLabs) for antibody capture. Phage clones are isolated from round 3 of screening for sequencing according to manufacturer's protocols. Unique clones are subsequently characterized by ELISA binding and inhibition assays.

Desirable peptides can be screened using the methods disclosed in PCT/US2008/001023, hereby incorporated herein by reference in their entirety. Briefly, a linear 12-mer and disulfide constrained 7-mer peptide phage display libraries are screened with pathogenic PF antibodies. Pools of phage-displayed peptides from the third round of selection is selected for specific binding to pathogenic PF antibodies by ELISA. Preparations of individual binding phage clones are isolated and their displayed peptide amino acid sequences are deduced by sequencing phage DNA.

Example 8: Using pathogenic and non-pathogenic antibodies to study the pathology of pemphigus foliaceus

The reagents disclosed herein, including pathogenic antibodies for PF should can be valuable to disrupt Dsg1 in keratinocytes. Without wishing to be bound by any

particular theory, it is believed that the pathogenic antibodies can be used to study pathways of desmoglein assembly into and disassembly from desmosomes. Targeting desmosomes and associated proteins can be candidates for therapy against skin fragility or susceptibility to blister formation in pemphigus patients.

The pathology of pemphigus foliaceus can be further studied by examining characteristics of desmosome assembly and dissasembly because desmosomes are adhesive junctions that contain transmembrane desmosomal cadherins, desmoglein and desmocollin. Both cadherins bind plakoglobin. Plakoglobin in turn binds desmoplakin, which links to the keratin intermediate filament (KIF) network. Adapter molecules such as plakophilin are believed to serve to increase the lateral adhesive strength of these junctions.

Without wishing to be bound by any particular theory, it is believed that pemphigus foliaceus autoantibodies can act upon non-desmosomal Dsg1, and therefore prevent incorporation of Dsg into the desmosome. Additionally or alternatively, antibodies could bind desmosomal Dsg1, which would be expected to lead to disassembly of Dsg1 from pre-formed desmosomes.

Keratinocytes are exposed to PF monoclonal antibodies at the time of the calcium switch. The effects of PF monoclonal antibody during desmosomal assembly can easily be evaluated by examining the localization of Dsg1 and desmoplakin. Conversely, if the cells are placed in calcium first, and PF monoclonal antibodies are subsequently added, the effects of PF monoclonal antibodies on desmosomal disassembly can similarly be examined by examining the localization of Dsg1 and desmoplakin.

It can also be determined whether the effects of Dsg1 parallel the loss of PF monoclonal antibodies from cell culture supernatants. "Assembly" is evaulated by exposing cells to calcium and PF monoclonal antibodies at the same time. The overall cell architecture of a cell in low and high calcium is represented by the cells shown can be assessed using standard immunohistochemical techniques. Without wishing to be bound by any particular theory, it is believed that cells treated with nonpathogenic antibodies, Dsg1 staining will not disrupted, but in cells treated with pathogenic antibodies, Dsg1 staining will remain diffusely cytoplasmic.

Having described preferred embodiments of the invention with reference to the accompanying drawings, it is to be understood that the invention is not limited to the precise embodiments, and that various changes and modifications may be effected therein by those skilled in the art without departing from the scope or spirit of the invention as defined in the appended claims.

The disclosures of each and every patent, patent application, and publication cited herein are hereby incorporated herein by reference in their entirety.

While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention. The appended claims are intended to be construed to include all such embodiments and equivalent variations.

What is claimed:

1. An isolated anti-desmoglein 1 (Dsg1) antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

2. The antibody or fragment thereof of claim 1, wherein the antibody is pathogenic and comprises a consensus sequence represented by Asp-X-X-X-Trp (SEQ ID NO: 259) or Glu-X-X-X-Trp (SEQ ID NO: 260).

3. The antibody or fragment thereof of claim 1, comprising a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

4. The antibody or fragment thereof of claim 1, comprising a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

5. The antibody or fragment thereof of claim 1, comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 44-86, and any combination thereof.

6. The antibody or fragment thereof of claim 1, wherein said antibody or fragment thereof is a single chain Fv (scFv), a Fab, a $(Fab')_2$ or a $(scFv')_2$.

7. A composition comprising an anti-autoimmune reagent, wherein said anti-autoimmune reagent specifically binds to an anti-desmoglein 1 (Dsg1) antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

8. The composition of claim 7, wherein said anti-autoimmune reagent is selected from the group consisting of a peptide, a small molecule, an antibody, a humanized antibody, a recombinant antibody, and any combination thereof.

9. The composition of claim 7, wherein said antibody or fragment thereof of comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

10. The composition of claim 7, wherein said antibody or fragment thereof of comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

11. The composition of claim 7, wherein said antibody or fragment thereof of comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 44-86, and any combination thereof.

12. An isolated nucleic acid sequence having at least 85% complementarity to a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

13. An inhibitor of an anti-desmoglein autoantibody or fragment thereof, wherein said inhibitor inhibits the expression of a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

14. The inhibitor of claim 13, wherein said inhibitor is selected from the group consisting of a small interfering RNA (siRNA), a microRNA, an antisense nucleic acid, a ribozyme, a polyamide, a triple-helix-forming agent, a synthetic peptide nucleic acids (PNAs), an agRNA, a LNA/DNA copolymer, and any combination thereof.

15. A method of inhibiting the binding of an anti-desmoglein 1 autoantibody or fragment thereof to desmoglein, said method comprising contacting the anti-desmoglein 1 autoantibody or fragment thereof with a composition comprising an anti-autoimmune reagent that specifically binds to an anti-desmoglein 1 autoantibody or fragment thereof.

16. The method of claim 15, wherein said anti-desmoglein 1 antibody or fragment thereof comprises a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

17. The method of claim 15, wherein the antibody or fragment thereof of comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

18. The method of claim 15, wherein the antibody or fragment thereof of comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

19. The method of claim 15, wherein the antibody or fragment thereof of comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 44-86, and any combination thereof.

20. The method of claim 15, wherein the antibody or fragment thereof is associated with the pathology of pemphigus foliaceus (PF).

21. A method of modulating the expression of an anti-desmoglein autoantibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof, said method comprising contacting a nucleotide sequence encoding said anti-desmoglein autoantibody or fragment thereof with an inhibitor of an anti-desmoglein autoantibody or fragment thereof, wherein said inhibitor is inhibits the expression of said anti-desmoglein autoantibody or fragment thereof.

22. The method of claim 20, wherein the nucleotide sequence encoding an anti-desmoglein autoantibody or fragment thereof is a sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

23. The method of claim 20, wherein the nucleotide sequence encoding an anti-desmoglein autoantibody or fragment thereof is at least 85% homology to a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

24. A method of treating an autoimmune pathology associated with pemphigus foliaceus (PF), the method comprising administering to a subject in need thereof a composition comprising an anti-autoimmune reagent that specifically binds to an anti-

desmoglein 1 autoantibody or fragment thereof, thereby inhibiting the binding of the anti-desmoglein 1 autoantibody or fragment thereof to desmoglein.

25. The method of claim 24, wherein said anti-desmoglein 1 antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

26. The method of claim 24, wherein said anti-autoimmune reagent is selected from the group consisting of a peptide, a small molecule, an antibody, a humanized antibody, a recombinant antibody, and any combination thereof.

27. The method of claim 24, wherein said antibody or fragment thereof of comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

28. The method of claim 24, wherein said antibody or fragment thereof of comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

29. The method of claim 24, wherein said antibody or fragment thereof of comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 1-43, and any combination thereof.

30. A method of treating an autoimmune pathology associated with pemphigus foliaceus (PF), the method comprising contacting a nucleotide sequence of the subject encoding an anti-desmoglein 1 antibody or fragment thereof with an inhibitor capable of inhibiting the expression of the nucleotide sequence encoding the anti-desmoglein autoantibody or fragment thereof, thereby inhibiting the expression of said anti-desmoglein autoantibody or fragment thereof.

31. The method of claim 30, wherein said anti-desmoglein 1 antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof

32. The method of claim 30, wherein the nucleotide sequence encoding an anti-desmoglein 1 autoantibody or fragment thereof is a sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

33. The method of claim 30, wherein the nucleotide sequence encoding an anti-desmoglein autoantibody or fragment thereof is at least 85% homology to a sequence selected from the group consisting of SEQ ID NOs: 1-43, 87-129, 130-172, and any combination thereof.

34. The method of claim 30, wherein said inhibitor is selected from the group consisting of a small interfering RNA (siRNA), a microRNA, an antisense nucleic acid, a ribozyme, a polyamide, a triple-helix-forming agent, a synthetic peptide nucleic acids (PNAs), an agRNA, a LNA/DNA copolymer, and any combination thereof.

35. A method of depleting a biological sample from an anti-desmoglein 1 antibody or fragment thereof, said method comprising contacting the sample with an immobile composition comprising an anti-autoimmune reagent capable of specifically binding to an anti-desmoglein 1 autoantibody or fragment thereof; and removing the biological sample without the bound anti-desmoglein 1 autoantibody or fragment thereof, thereby depleting the biological sample of anti-desmoglein 1 autoantibody or fragment thereof.

36. The method of claim 35, wherein said anti-desmoglein 1 antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof

37. The method of claim 35, wherein the anti-desmoglein autoantibody or fragment thereof is associated with the pathology of pemphigus foliaceus (PF).

38. The method of claim 35, wherein said anti-desmoglein 1 autoantibody or fragment thereof comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

39. The method of claim 35, wherein said anti-desmoglein 1 autoantibody or fragment thereof comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

40. The method of claim 35, wherein said anti-desmoglein 1 autoantibody or fragment thereof comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 1-43, and any combination thereof.

41. The method of claim 35, wherein the step of contacting the sample with an immobile composition is carried out during a plasmapheresis procedure performed on a subject.

42. A method of diagnosing pemphigus foliaceus (PF) in a subject, the method comprising contacting a biological sample of said subject with a composition comprising an anti-autoimmune reagent that specifically binds to an anti-desmoglein 1 autoantibody or fragment thereof; and analyzing the biological sample for the presence of antibody-antigen complex, whereby the presence of antibody-antigen complex indicates the subject has or is predisposed to pemphigus foliaceus (PF).

43. The method of claim 42, wherein said anti-autoimmune reagent specifically binds to an anti-desmoglein 1 (Dsg1) antibody or fragment thereof comprising a heavy chain (V_H) encoded by the gene selected from the group consisting of VH1-18, VH1-08, VH3-09, VH3-07, VH3-30, VH4-b, VH3-53, VH3-66, and any combination thereof.

44. The method of claim 42, wherein said anti-autoimmune reagent is selected from the group consisting of a peptide, a small molecule, an antibody, a humanized antibody, a recombinant antibody, and any combination thereof.

45. The method of claim 42, wherein said antibody or fragment thereof of comprises a heavy chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 216-258, and any combination thereof.

46. The method of claim 42, wherein said antibody or fragment thereof of comprises a light chain variable domain comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 173-215, and any combination thereof.

47. The method of claim 42, wherein said antibody or fragment thereof of comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 1-43, and any combination thereof.

48. The method of claim 42, wherein said contacting the biological sample with the composition comprising an anti-autoimmune reagent is evaluated using a radio-immunoassay (RIA), an enzyme linked immunosorbent assay (ELISA), a western blot, an immunohistochemical analysis, or a combination thereof.

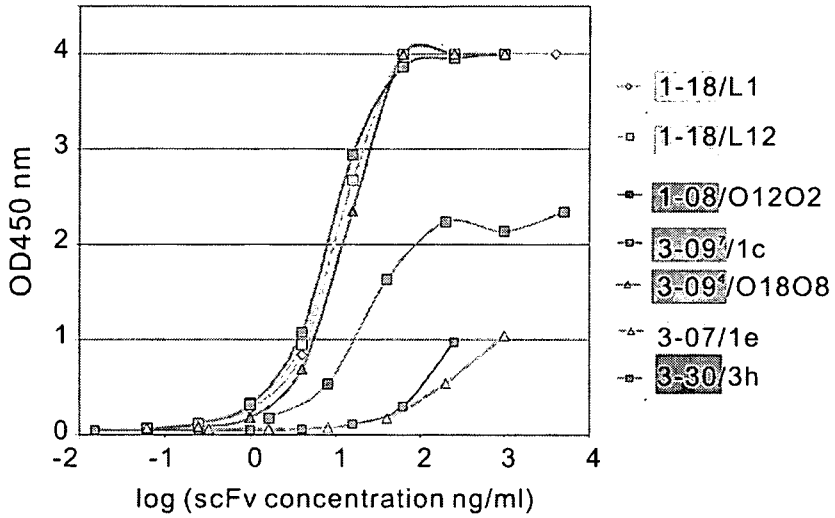
OD450 nm
4
3
2
1
0
-2
-1
0
1
2
3
4
log (scFv concentration ng/ml)
1-18/L1
1-18/L12
1-08/O12O2
3-09/1c
3-09/O18O8
3-07/1e
3-30/3h

FIGURE 1

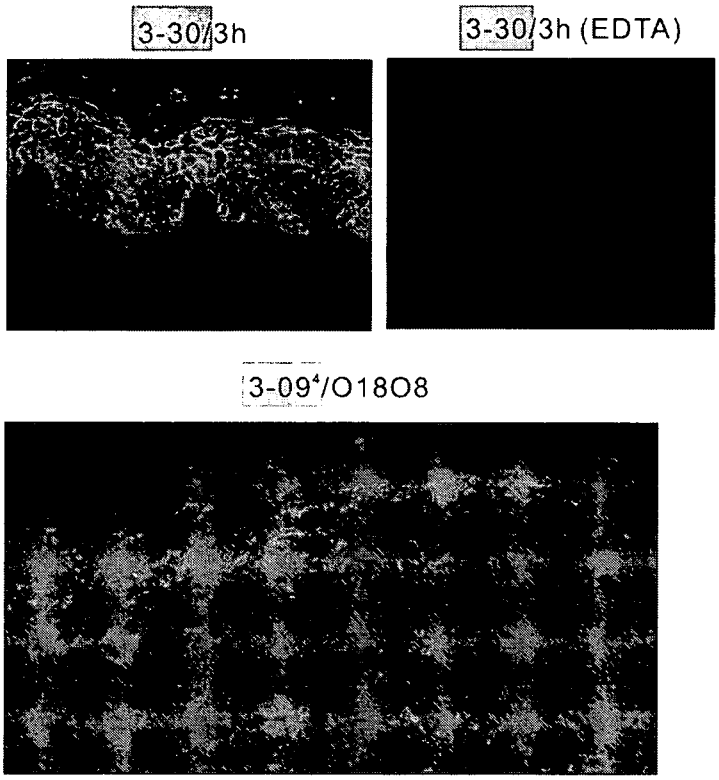

FIGURE 2

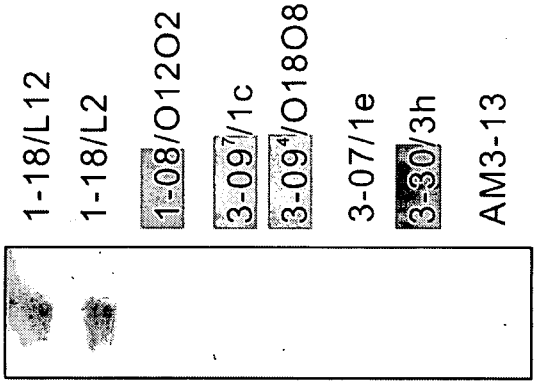

FIGURE 3A

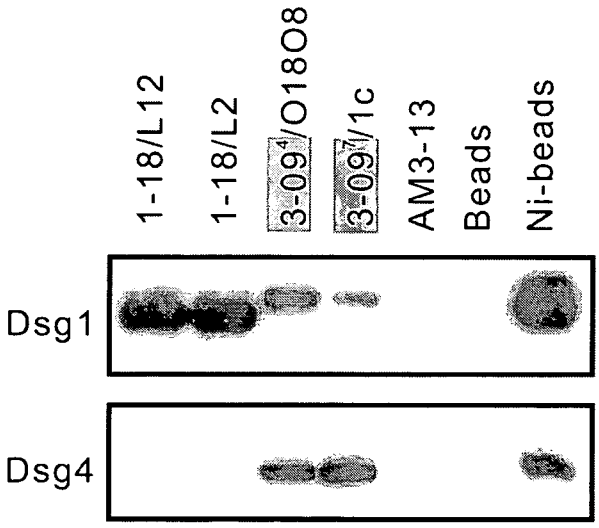

FIGURE 3B

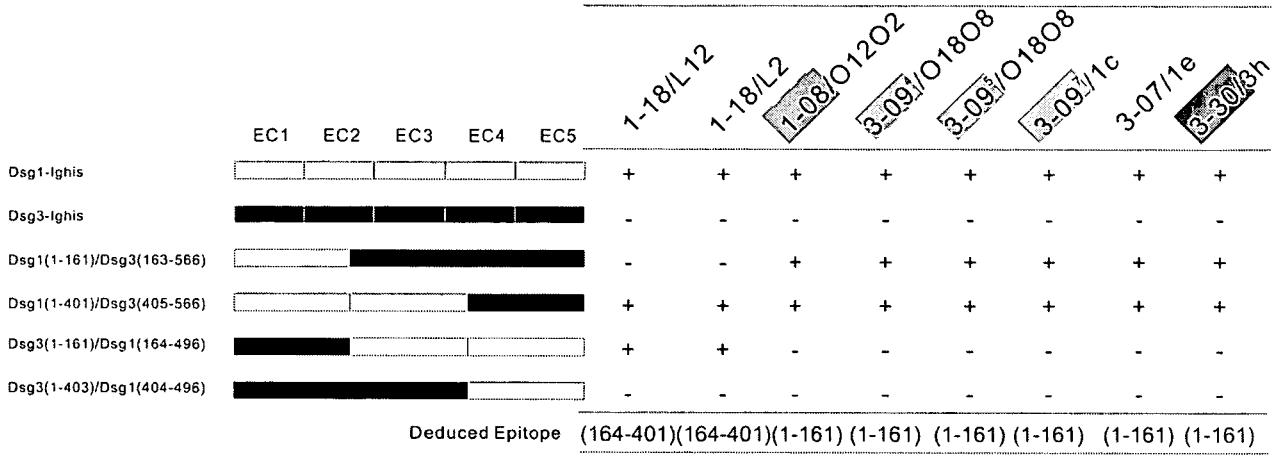
EC1
EC2
EC3
EC4
EC5
1-18/L12
1-18/L2
1-08/O12O2
3-09/O18O8
3-09/O18O8
3-09/1c
3-07/1e
3-30/3h
Dsg1-Ighis + + + + + + + +
Dsg3-Ighis - - - - - - - -
Dsg1(1-161)/Dsg3(163-566) - - + + + + + +
Dsg1(1-401)/Dsg3(405-566) + + + + + + + +
Dsg3(1-161)/Dsg1(164-496) + + - - - - - -
Dsg3(1-403)/Dsg1(404-496) - - - - - - - -
Deduced Epitope (164-401)(164-401)(1-161) (1-161) (1-161) (1-161) (1-161) (1-161)

FIGURE 4

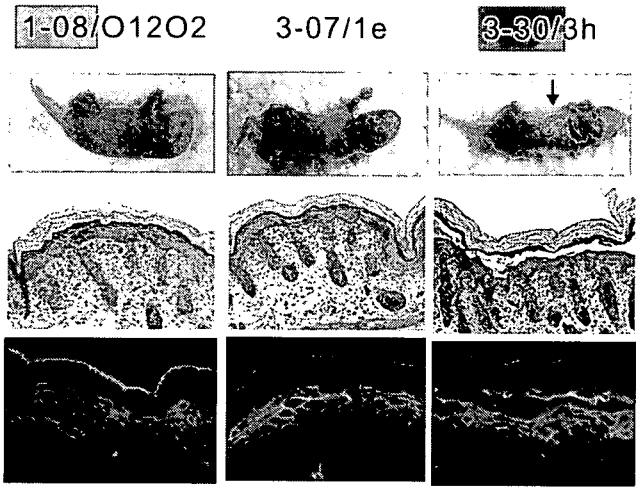

FIGURE 5A

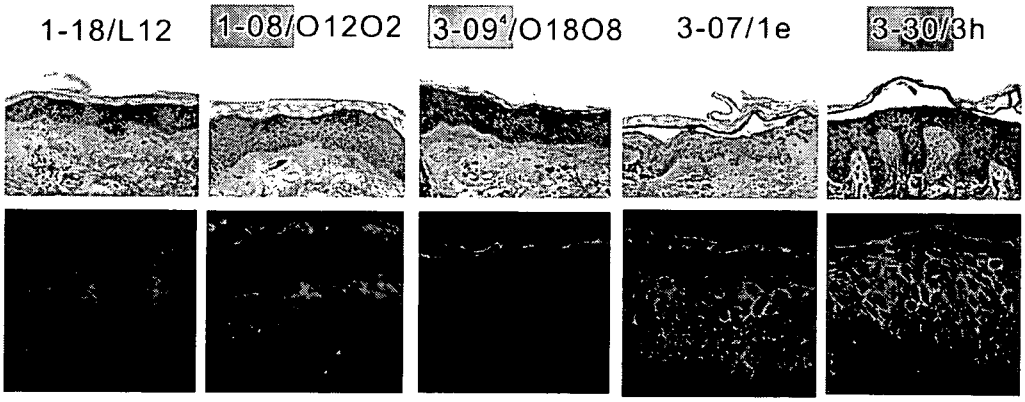

FIGURE 5B

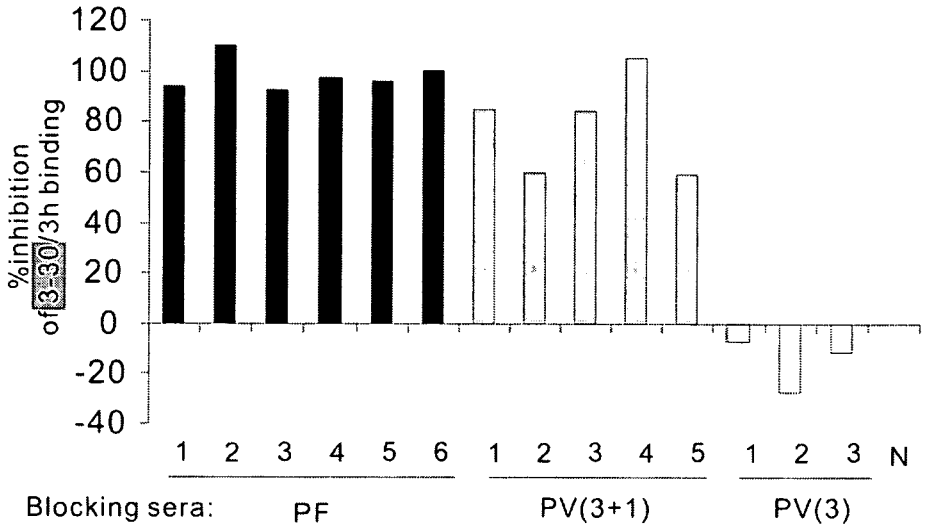

FIGURE 6A

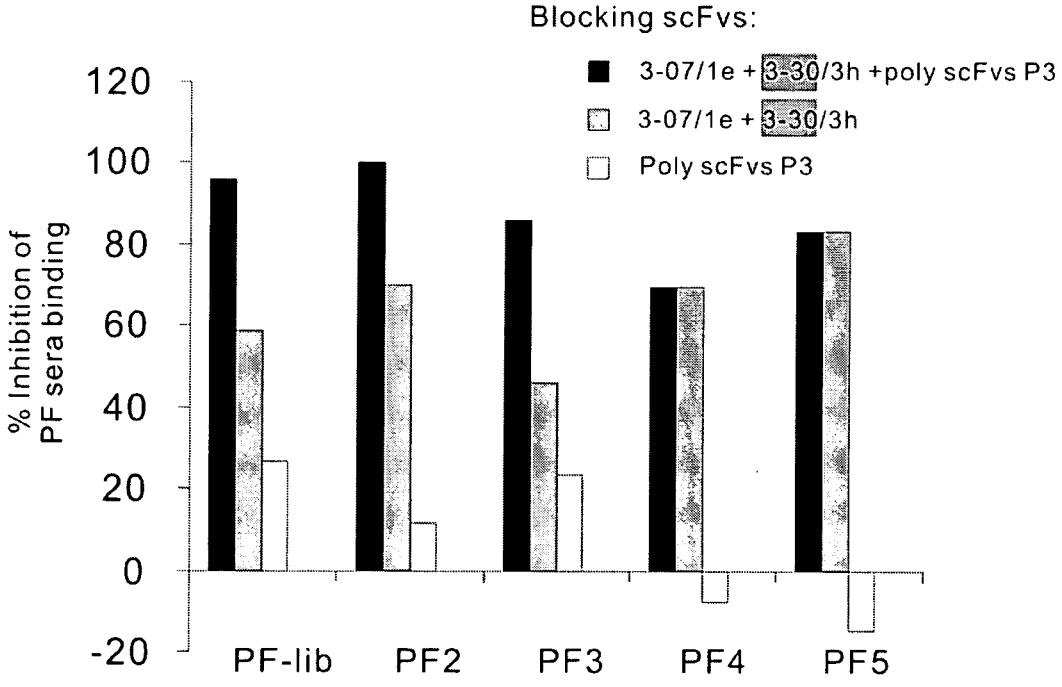

FIGURE 6B

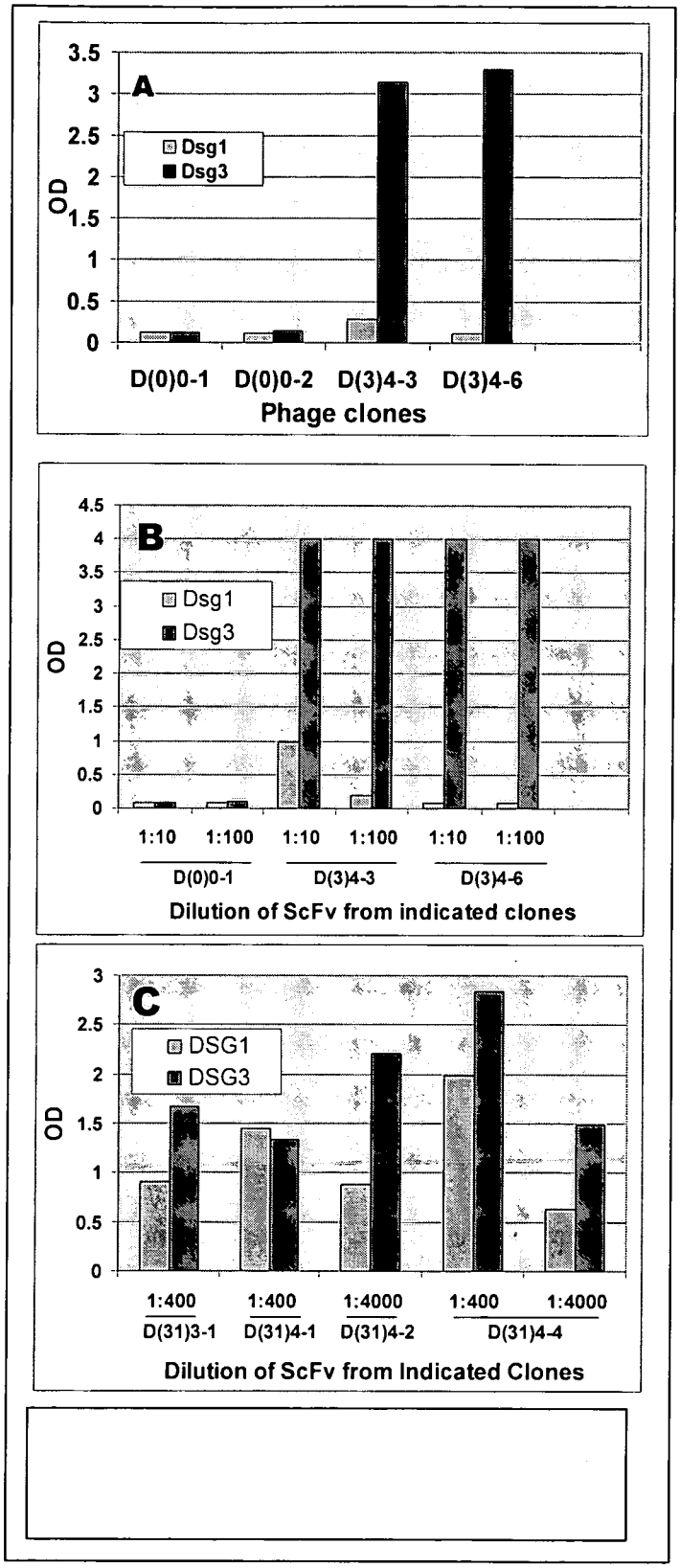
A
Dsg1
Dsg3
OD
3.5
3
2.5
2
1.5
1
0.5
0
D(0)0-1
D(0)0-2
D(3)4-3
D(3)4-6
Phage clones
B
Dsg1
Dsg3
OD
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1:10
1:100
1:10
1:100
1:10
1:100
D(0)0-1
D(3)4-3
D(3)4-6
Dilution of ScFv from indicated clones
C
DSG1
DSG3
OD
3
2.5
2
1.5
1
0.5
0
1:400
1:400
1:4000
1:400
1:4000
D(31)3-1
D(31)4-1
D(31)4-2
D(31)4-4
Dilution of ScFv from Indicated Clones

FIGURE 7

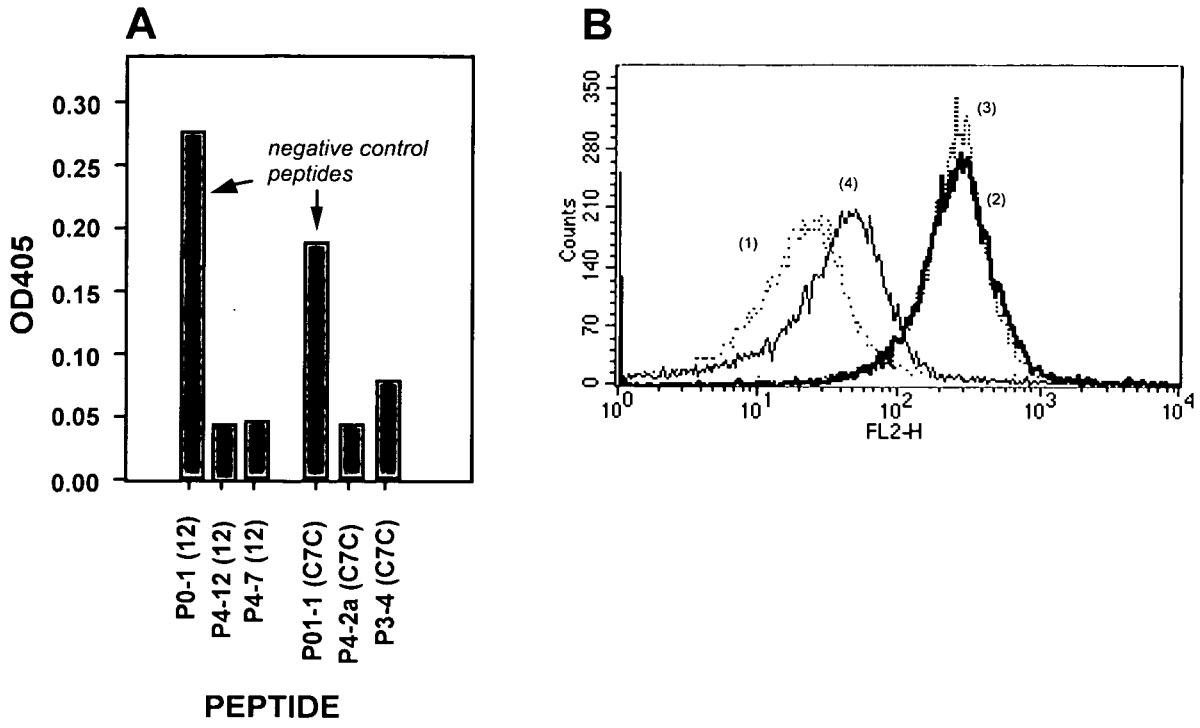
A
0.30
0.25
0.20
0.15
0.10
0.05
0.00
OD405
negative control peptides
P0-1 (12)
P4-12 (12)
P4-7 (12)
P01-1 (C7C)
P4-2a (C7C)
P3-4 (C7C)
PEPTIDE
B
Counts
350
280
210
140
70
0
(1)
(2)
(3)
(4)
10^0
10^1
10^2
10^3
10^4
FL2-H

FIGURE 8

Figure 9A-1

scFv name(s)	Desmoglein Specificity	DNA Seq ID	AA Seq ID	Heavy chain genes (V/D/J)	Light chain genes (V/J)
PF1-2-7, 1-18/B3	Dsg-1	#1	#44	VH1-18/D3-10/JH4b	B3/JK4
PF1-2-1, 1-18/L8	Dsg-1	#2	#45	VH1-18/D3-10/JH4b	L8/JK2
PF1-2-5, 1-18/L1	Dsg-1	#3	#46	VH1-18/D3-10/JH4b	L1/JK3
PF1-2-6, 1-18/L12	Dsg-1	#4	#47	VH1-18/D3-10/JH4b	L12/JK4
PF1-3-K11, 1-18/L2	Dsg-1	#5	#48	VH1-18/D3-10/JH4b	L2/JK2
PF1-2-15, 1-18/LFVK431	Dsg-1	#6	#49	VH1-18/D3-10/JH4b	LFVK431/JK4
PF1-2-22, 1-08/01202	Dsg-1	#7	#50	VH1-08/D3-3/JH6b	O12/JK4
PF1-2-11, 3-09^3/01202	Dsg-1	#8	#51	VH3-09/D2-2/JH6b	O12/JK5
PF1-2-17, 3-09^3/01808	Dsg-1	#9	#52	VH3-09/D2-2/JH6b	O18/JK4
PF1-29, 3-09^3/L11	Dsg-1	#10	#53	VH3-09/D2-2/JH6b	L11/JK1
PF1-1-35, PF1-35, 3-09^3/A30	Dsg-1	#11	#54	VH3-09/D2-2/JH6b	A30/JK1
PF1-2-L19, 3-09^3/1c	Dsg-1	#12	#55	VH3-09/D2-2/JH6b	1c/JL2
PF1-2-L32, 3-09^3/1e	Dsg-1	#13	#56	VH3-09/D2-2/JH6b	1e/JL2
PF1-2-L4, 3-09^3/1g	Dsg-1	#14	#57	VH3-09/D2-2/JH6b	1g/JL2
PF1-2-L10, 3-09^3/6a	Dsg-1	#15	#58	VH3-09/D2-2/JH6b	6a/JL3b
PF1-2-10, 3-09^4/01808	Dsg-1	#16	#59	VH3-09/D3-3/JH3a	O18/JK3
PF1-2-9, 3-09^5/01808	Dsg-1	#17	#60	VH3-09/D3-3/JH3a	O18/JK3
PF1-3-K6, 3-09^5/L11	Dsg-1	#18	#61	VH3-09/D3-3/JH3a	L11/JK2
PF1-26, 3-09^6/L12	Dsg-1	#19	#62	VH3-09/D3-3/JH3a	L12/JK1
PF1-22, 3-09^6/01808	Dsg-1	#20	#63	VH3-09/D3-3/JH3a	O18/JK3
PF1-2-L02, 3-09^6/1c	Dsg-1	#21	#64	VH3-09/D3-3/JH3a	1c/JL2
PF1-2-3, PF1-2-03, 3-09^7/1c	Dsg-1	#22	#65	VH3-09/D3-3/JH3b	1c/JL2
PF1-2-18, 3-	Dsg-1	#23	#66	VH3-09/D3-22/JH4b	L11/JK3

09[8]/L11					
PF1-1-7, PF1-07, 3-09[9]/L8	Dsg-1	#24	#67	VH3-09/D2-8/JH2	L8/JK1
PF1-19, 3-09[9]/L2	Dsg-1	#25	#68	VH3-09/D2-8/JH2	L2/JK5
PF1-8-2, PF1-8-5, 3-07/1e	Dsg-1	#26	#69	VH3-07/D3-10/JH4b	1e/JL3b
PF1-8-15, 3-30/3h	Dsg-1	#27	#70	VH3-30/D5-24/JH4b	3h/JL2
F24-1	Dsg-1	#28	#71	VH4-b/D3-10/JH3b	3r/JL3b
F24-2, F24-6, F24-13, F24-16	Dsg-1	#29	#72	VH3-30/D6-13/JH4d	3j/JL2
F24-3, F24-7, F23-1,	Dsg-1	#30	#73	VH3-09/D3-3/JH3b	1c/JL7
F24-4, F23-4	Dsg-1	#31	#74	VH3-09/D3-3/JH3a	L5/JK5
F24-5, F24-8, F24-14, F23-2, F23-3, F23-10, F23-12, F23-13	Dsg-1	#32	#75	VH3-09/D3-3/JH3b	018/JK4
F24-9	Dsg-1	#33	#76	VH3-53/D4/JH4b	1c/JL3b
F24-11	Dsg-1	#34	#77	VH3-09/D3-3/JH3b	1c/JL3b
F24-15	Dsg-1	#35	#78	VH3-66/D7-27/JH4b	1c/JL3b
F23-5	Dsg-1	#36	#79	VH1-08/D3-10/JH6b	4b/JL3b
F23-6	Dsg-1	#37	#80	VH3-09/D3-22/JH3b	L11/JK4
F23-7	Dsg-1	#38	#81	VH3-09/D3-3/JH3a	1e/JL3b
F23-8	Dsg-1	#39	#82	VH3-09/D3-3/JH3b	012/JK5
F23-9	Dsg-1	#40	#83	VH3-09/D2-8/JH2	1c/JL2
F23-14	Dsg-1	#41	#84	VH3-09/D3-3/JH3b	1c/JL2
F23-15	Dsg-1	#42	#85	VH3-30/D4-b/JH4b	012/JK5
F23-16	Dsg-1	#43	#86	VH3-09/D3-3/JH3b	1c/JL3b

Figure 9A-2

Figure 9B-1: SEQ ID #1

GAGCTCGTGTTGACACAGTCTCCAGACTCCCTGTCTGTGTCTCTGGGCGAGAGGGCC
ACCATCAACTGCAAGTCCAGCCAGACTGTTTTATACAACTCCGACAATAAGAACTAC
TTAAGTTGGTACCAGCAGAAACCAGGACAGCCTCCTAAGTTGATCATGAACTGGGCA
TCTATCCGGGCATCCGGGGTCCCTGACCGATTCAGTGGCAGCGGGTCTGGGACAGAT
TTCACTCTCACCATCAACAGCCTGCAGGCTGAAGATGTGGCAATTTATTACTGTCAGC
AATATTATAGTACTCCGCTCACCTTCGGCGGAGGGACCAAGGTGGAAATCAAA**GGT**
GGTTCCTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTG
GTGGGCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTT
AGTGAAGGTCTCCTGCAAGGCTTCTGGTTACACGTTTACCAATTATGGTATCACCTGG
GTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGATGGATCAGTGTTTATAAT
GGTGACACAAAGTATGCACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACAC
GCCCACGAACACAGTGTATATGGAGTTGAGGAGCCTGAGATCTGACGACACGGCCG
TGTATTATTGTGCGAGAGGTTATGGTTCGGGGAATTGGGACTACTGGGGCCAGGGAA
CCCTGGTCACCGTCTCCTCAG

Figure 9B-2: SEQ ID #2

GAGCTCACACTCACGCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCCAGTCAGGGCATTGCCAGTTATTTAGCCTGGTATCAGCAA
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGGTGCATCCACTTTGCAAAGTGGG
GTCCCATCAAGGTTCAGCGGCCGTAGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATGCTGCAACTTATTACTGCCAACAATATAGTAATTACCCT
CTGACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGC
TGGTGCAGTCTGGAGCTGAGATGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCA
AGGCTTCTGGTTACACCTTTACCAATTATGGTATCACCTGGGTGCGACAGGCCCCTGG
ACAAGGGCTTGAGTGGATGGGATGGATCAGTGTTTATAATGGTGACACAAAGTATGC
ACAGAAGCTCCAGGGCAGAGTCACTATGACCACAGACACACCCACGAGCACAGTCT
ACATGGAATTGAGGAGCCTGACATCTGACGACACGGCCGTGTATTATTGTGTGAGAG
GTTATGGTTCGGGGAATTGGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCT
CAG

Figure 9B-3: SEQ ID #3

GAGCTCCAGATGACCCAGTCTCCATCCTCACTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGTCGGGCGAGTCAGGGCATTAACAATTATTTAGCCTGGTTTCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAAGGCGTCTAGTTTAGAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGTATAATAGTTACCCAT
TCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA**GGTGGTTCCTCTAGATCT**
TCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGCTG
GTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAA
GGCTTCTGGTTACACGTTTACCAATTATGGTATCACCTGGGTGCGACAGGCCCCTGG
ACAAGGGCTTGAGTGGATGGGATGGATCAGTGTTTATAATGGTGACACAAAGTATGC
ACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACGCCCACGAACACAGTGT
ATATGGAGTTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTATTGTGCGAGAG
GTTATGGTTCGGGGAATTGGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCT
CAG

Figure 9B-4: SEQ ID #4

GAGCTCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAACTGGTTAGCCTGGTATCAGCAG
AAACCAGGAAAAGCCCCTAAGCTCCTGATCCATAAGGCATCTAGTTTAGAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGTATTATACTTACCCGC
TCACTTTCGGCGGAGGGACCAAGGTGGAAATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGC
TGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCA
AGGCTTCTGGTTACACGTTTACCAATTATGGTATCACCTGGGTGCGACAGGCCCCTG
GACAAGGGCTTGAGTGGATGGGATGGATCAGTGTTTATAATGGTGACACAAAGTATG
CACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACGCCCACGAACACAGTG
TATATGGAGTTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTATTGTGCGAGA
GGTTATGGTTCGGGGAATTGGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCC
TCAG

Figure 9B-5: SEQ ID #5

GAGCTCGTGTTGACGCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAATTTAGCCTGGTACCAGCAG
AAACCTGGCCAGGCTCCCAGGCTCCTCATCAAAGGAGCATCCACCAGGGCCACTGGT
ATCCCAGACAGGTTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGGCTGAAGATGTGGCAGTTTACTACTGTCACCAGTATTATGGTCCTTACT
CTTTTGGCCAGGGGACCAAGGTGGAAATCAAA**GGTGGTTCCTCTAGATCTTC**
CTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGCTGGT
GCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGC
TTCTGGTTACACGTTTACCAATTATGGTATCACCTGGGTGCGACAGGCCCCTGGACA
AGGGCTTGAGTGGATGGGATGGATCAGTGTTTATAATGGTGACACAAAGTATGCACA
GAAGCTCCAGGGCAGAGTCACCATGACCACAGACACGCCCACGAACACAGTGTATA
TGGAGTTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTATTGTGCGAGAGGTT
ATGGTTCGGGGAATTGGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG

Figure 9B-6: SEQ ID #6

GAGCTCCAGATGACCCAGTCTCCATCCTCACTGTCTGCATCTGTTGGAGACAGAGTC
ACCATCACTTGTCGGGCGACTCAGGGCATTAGTAATTATTTAGCCTGGTTTCAGCAG
AAACCAGGGAAAGCCCCTAAGTTGCTGATCTATGCTGCATCCAGTTTGCAAAGTGGG
GTCCCATCAAAGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGCCAACAGTATAATAGTTATCCTC
TCACTTTCGGCGGAGGGACCAAGGTGGAAATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGC
TGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCA
AGGCTTCTGGTTACACGTTTACCAATTATGGTATCACCTGGGTGCGACAGGCCCCTG
GACAAGGGCTTGAGTGGATGGGATGGATCAGTGTTTATAATGGTGACACAAAGTATG
CACAGAAGCTCCAGGGCAGAGTCACCATGACCACAGACACGCTCACGAACACAGTG
TATATGGAGTTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTATTGTGCGAGA
GGTTATGGTTCGGGGAATTGGGACTACTGGGGCCAGGGAACCCCGGTCACCGTCTCC
TCAG

Figure 9B-7: SEQ ID #7

GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGG
GTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTC
GCACTTTCGGCGGAGGGACCAAGCTGGAGATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGC
TGGTGCAGTCTGGGGCTGAGGTGAGGAAGCCTGGGGCCTCAGTGAGGGTCTCCTGCA
AGGCTTCTGGATACACCCTCACCACTTATGATATCAACTGGGTGCGACAGGCTACTG
GACAAGGGCTTGAGTGGATGGGATGGATGAACCCTACCAGTGGTAACACAGCCTAC
GCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAACACCTCCATAAGCACAGC
CTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTTTACTACTGTGCGAG
AGGCCTGTTTTTTGGAGTGGTTACAAAACCCAACTACTACTACTACGCTATGGACGTC
TGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-8: SEQ ID #8

GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGTATCAGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGAGCATTAGCGGCTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAACTGCTGATCTATGGTGCATCCAGTTTGCAAAGTGGG
GTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCGCTCTCACCATCAGC
AGTGTGCAACCTGAAGATTTTGCAAGTTACTTCTGTCAACAGAGTCACAGCGTCCCG
ATCAACTTCGGCCAAGGGACACGACTGGAGATTAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGC
TGGTGCAGTCTGGGGGAGGCTTGGCACAGCCTGGCAAGTCCCTGAGACTCTCCTGTG
TAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGG
GAAGGGCCTGGAGTGGGTCTCAGGTATTAATTGGAATAGTGGTAGCATTGGTTATGC
GGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTA
TCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGA
GCAAGGATATTGTGATAGTACCGGCTGCCAGAGGGGATCCGGAATGGACGTCTGGG
GCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-9: SEQ ID #9

GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCAGGCGAGTCAGGACATTAGCAACTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTACGATGCATCCAATTTGGAAACAGGG
GTCCCATCAAGGCTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCACCATCAGC
AGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGATGATCTCCCC
CTCACTTTCGGCGGAGGGACCAAGCTGGAGATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGC
TGGTGCAGTCTGGGGGAGGCTTGGCACAGCCTGGCAAGTCCCTGAGACTCTCCTGTG
TAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGG
GAAGGGCCTGGAGTGGGTCTCAGGTATTAATTGGAATAGTGGTAGCATTGGTTATGC
GGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTA
TCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGA
GCAAGGATATTGTGATAGTACCGGCTGCCAGAGGGGATCCGGAATGGACGTCTGGG
GCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-10: SEQ ID #10
GAGCTCCAGATGACCCAGTCTCCATCGTCCCTGGCTGCATCTGTGGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCACGACATTAAAAATGATTTAGGCTGGTATCAGCAT
CAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTACAAAGTGGG
GTCCCGTCAAGATTCAGCGGCAGTGGATCCGGCACAAATTTCACCCTCACCATCAAT
AGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACATGATTACACTTACCCTC
GCACGTTCGGCCAAGGGACCAAGGTGGAAATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGC
TGGTGCAGTCTGGGGGAGGCTTGGCACAGCCTGGCAAGTCCCTGAGACTCTCCTGTG
TAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGG
GAAGGGCCTGGAGTGGGTCTCAGGTATTAATTGGAATAGTGGTAGCATTGGTTATGC
GGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTA
TCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGA
GCAAGGATATTGTGATAGTACCGGCTGCCAGAGGGGATCCGGAATGGACGTCTGGG
GCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-11: SEQ ID #11
GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGGGCATTAGATATGATGTAGGCTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCACCTTGCAAAGTGGG
GTCCCATCAAGGTTCAGTGGCAGCGGATCTGAGACAGATTTCACTCTCACCATCAAC
AGTCTGCAGCCTGAAGATTCTGCAACTTACTACTGTCAACAGAGTTACAGTATCCCTT
CGACGTTCGGCCAGGGGACCAAGGTGGAGATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGC
TGTTGGAGTCTGGGGGAGGCTTGGCACAGCCTGGCAAGTCCCTGAGACTCTCCTGTG
TAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGG
GAAGGGCCTGGAGTGGGTCTCAGGTATTAATTGGAATAGTGGTAGCATTGGTTATGC
GGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTA
TCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGA
GCAAGGATATTGTGATAGTACCGGCTGCCAGAGGGGATCCGGAATGGACGTCTGGG
GCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-12: SEQ ID #12
GAGCTCGAGCTGACTCAGCCACCCTCAGTGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTGATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCAGTCTGAGGATGAGGCTGACTATTACTGTGCAACATGGGATGACGGCC
TGCGTGGCATGGTGTTCGGCGAAGGCACCAAGCTGACCGTCCTAGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGCACAGCCTGGCAAGTCCCTGAG
ACTCTCCTGTGTAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGG
CAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAATTGGAATAGTGGTAGC
ATTGGTTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAG
AACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTAC
TGTGCAAAAGAGCAAGGATATTGTGATAGTACCGGCTGCCAGAGGGGATCCGGAAT
GGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-13: SEQ ID #13
GAGCTCGTGTTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCGGAGGGTCACC
ATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCTGCTTATGATGTACACTGGTAC
CAGCAGCTTCCAGGAACAGCCCCCAAACTCCTCATCTTTGGTAACACCAATCGGCCC
TCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA
TCACTGGGCTCCAGTCTGAGGATGAGGCTGACTATTACTGTGCAACATGGGATGACA
GCCGGGATGGTCCGGAAGTGGTGTTCGGCGGAGGCACCGAGCTGACCGTCCTCGGT
GGTGGTTCCTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCG
GTGGTGGGGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGCACAGCCTGGCA
AGTCCCTGAGACTCTCCTGTGTAGCCTCTGGATTCACCTTTGATGATTATGCCATGCA
CTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAATTGGAA
TAGTGGTAGCATTGGTTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGA
CAACGCCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGG
CCTTGTATTACTGTGCAAAAGAGCAAGGATATTGTGATAGTACCGGCTGCCAGAGGG
GATCCGGAATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-14: SEQ ID #14
GAGCTCGTGCTGACTCAGCCACCTTCGGCGTCTGGGACCCCCGGACAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAACTCCAACATCGGAAGTGATTATGTGTACTGGTATCAGC
GGTTCCCAGGAACGGCCCCCAAACTTCTCATCTATAGTAATAATCAGCGGCCCTCAG
GGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAG
TGGACTCCAGTCTGAGGATGAGGCTGAGTATTACTGTGCAACATGGGATGACGCCCT
GCGTGGCATGGTGTTCGGCGAAGGCACCAAGCTGACCGTCCTAGGT**GGTGGTTCC**
TCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGG
AGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGCACAGCCTGGCAAGTCCCTGAGA
CTCTCCTGTGTAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGC
AAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAATTGGAATAGTGGTAGC
ATTGGTTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAG
AACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTAC
TGTGCAAAAGAGCAAGGATATTGTGATAGTACCGGCTGCCAGAGGGGATCCGGAAT
GGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-15: SEQ ID #15
GAGCTCATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACC
ATCTCCTGCACCCGCAGCAGTGGCAGCATTGCCAGCAACTTTGTCCAGTGGTACCAG
CAGCGCCCGGGCAAGTCCCCCACCACTGTAATTTATGAGGACAACCAAAGACCGTCT
GGGGTACCTGATCGGTTCTCTGGCTCCGTCGACAGGTCCTCCAACTCTGCCTCCCTCA
CCATCTCTGGACTGCAGACTGAGGACGAGGCTGACTATTACTGTCAGTCTTTTTATGA
CGGCGTCCCTTCTTGGGTGTTCGGCGGAGGCACCGAGCTGACCGTCCTCGGC**GGTG**
GTTCCTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGG
TGGGGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAACCTGGGGGGTCC
CTAAGACTCTCCTGTGTAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGG
TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAATTGGAATAGTG
GTAGCATTGGTTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACG
CCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGT
ATTACTGTGCAAAAGAGCAAGGATATTGTGATAGTACCGGCTGCCAGAGGGGATCC
GGAATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAG

Figure 9B-16: SEQ ID #16
GAGCTCATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCGGGGAAGACGGTAACC
ATCTCCTGCACCCGCAGCAGTGGCAGCATTGCCAGCAACTTTGTCCAGTGGTACCAG
CAGCGCCCGGGCAAGTCCCCCACCACTGTAATTTATGAGGACAACCAAAGACCGTCT
GGGGTACCTGATCGGTTCTCTGGCTCCGTCGACAGGTCCTCCAACTCTGCCTCCCTCA
CCATCTCTGGACTGCAGACTGAGGACGAGGCTGACTATTACTGTCAGTCTTTTTATGA
CGGCGTCCCTTCTTGGGTGTTCGGCGGAGGCACCGAGCTGACCGTCCTCGGC**GGTG**
GTTCCTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGG
TGGGCAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGGGGTCC
CTGAGACTCTCCTGTGTAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGG
TCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTG
GTGCCATAGGCTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACG
CCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAACTGAGGACACGGCCGTGT
ATTACTGTGCAAAAGATGGGATTACAATTTTTGGAGTGGGCGACGGTCTGGATGTCT
GGGGCCAAGGGACAATGGTCACCGTCTCTTCAG

Figure 9B-17: SEQ ID #17
GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCAGGCGAGTCAGGACATTGGCAACTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAACTCCTGATCTACGATGCATCCTATTTGGAAACAGGG
GTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCACCATCAGC
AGCCTACAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGATAATCTCCCG
TTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGC
TGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTG
CAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAG
GGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGACTATG
CGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGT
ATCTGCAAATGAACAGTCTGAGAGTTGAGGACACGGCCTTGTATTATTGTGCAAAAG
ATGGGAGTAGGGTTTTTGGAGTGGGCGGTGGTTTTGATTTCTGGGGCCAAGGGACAA
TGGTCACCGTCTCTTCAG

Figure 9B-18: SEQ ID #18
GAGCTCGTGATGACTCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGGGCATTACCGATGACTTAGGGTGGTATCAGCAG
AAGCCAGGGAAAGCCCCTAAGCTCCTGATCTATGCCACATCCAATTTAGAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGACACAGAATTCACTCTCACCATCAGT
AGCCTGCAGCCTGAAGATCTTGCAACTTATTACTGTCTACAAGATTACAGTTACCCGT
ACACTTTTGGCCAGGGGACCAAGGTGGAGATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGC
TAGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTG
CAGCCTCTGGATTCACCTTTGATGATTACGCCATGCACTGGGTCCGGCAAGCTCCAG
GGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGACTATG
TGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTACCTGT
ATCTGCAAATGAACAGTCTGAGAGTTGAGGACACGGCCTTATATTATTGTGCAAAAG
ATGGCAGTAGGGTTTTTGGAGTGGGCGGTGGTTTTGATTTCTGGGGCCAAGGGACAA
TGGTCACCGTCTCTTCAG

Figure 9B-19: SEQ ID #19
GAGCTCCAGATGACCCAGTCTCCTTCCACCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCCAGTCAGAGTATTAGTAGTTGGTTGGCCTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATAAGGCGTCTAGTTTAGAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGTATAATACTTATTCGA
GGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGC
TGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTG
CAGCCTCTGGATTCACCTTTGATGATTATTCCATGCACTGGGTCCGGCAAGCTCCAGG
GAAGGGCCTGGAGTGGGTCTCAGGTATCAGTTGGAACAGTGGTGGCATAGGCTATGC
GGACTCTGTGAGGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTA
TCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTATTGTGCAAAAGA
TGGGATGAGGGTTTTTGGAGTGGGCGGTGGTTTTGATTTCTGGGGCCAAGGGACAAT
GGTCACCGTCTCTTCAG

Figure 9B-20: SEQ ID #20
GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGACAGAGTC
ACCATCACTTGCCAGGCGAGTCGTGACATTAGCAACTATTTAAATTGGTATCAACAC
ATTCCAGGAAAGGCCCCTAAGCTCCTCATATTCCATGCATCCACTTTGGAAGCAGGG
ATCCCATCAAGGTTCAGTGGAAGTGGATCAGAGACATCTTTTACTTTCACCATAAGA
AGCCTACAGCCTGAAGATGTTGCAACATATTACTGTCAACAATATGATAATCTCCCC
TTCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGC
TGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTG
CAGCCTCTGGATTCACCTTTGATGATTATGCCATGTACTGGGTCCGGCAAGCTCCAGG
GAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGACTATGC
GGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTA
TCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTATTGTGCAAAAGA
TGGGATGAGGGTTTTTGGAGTGGGCGGTGGTTTTGATTTCTGGGGCCAAGGGACAAT
GGTCACCGTCTCTTCAG

Figure 9B-21: SEQ ID #21
GAGCTCATGCTGACTCAGCCCCACTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCC
TGAATGGTCCGGTATTCGGCGGAGGCACCAAGGTGACCGTCCTAGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAG
ACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGTACTGGGTCCGG
CAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGC
ATAGACTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAG
AACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTAT
TGTGCAAAAGATGGGATGAGGGTTTTTGGAGTGGGCGGTGGTTTTGATTTCTGGGGC
CAAGGGACAATGGTCACCGTCTCTTCAG

Figure 9B-22: SEQ ID #22
GAGCTCGTGGTGACGCAGCCGCCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAACGTGGGATGACGGCC
TGAATGGCATGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAG
ACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGG
CAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGGAC
CATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAA
GAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTGTATTA
CTGTGCAAAAGATGGGATTACGGTTTTTGGAGTGGGCGATGGTTTGGATATCTGGGG
CCAAGGGACAATGGTCACCGTCTCTTCAG

Figure 9B-23: SEQ ID #23
GAGCTCCAGATGACCCAGTCTCCTTCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGGGCATTGGAAATGATTTAGGCTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTACAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGGCACAGATTTCACTCTCACCATCGGC
AGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAAGATTACAATTACCCAT
TCACTTTCGGCCCTGGGACCAAAGTGGATATCAAA**GGTGGTTCCTCTAGATCT**
TCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGCT
GGTGGAGTCTGGGGGAACCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGC
AGCCTCTGGATTCAGCTTTGATGATTATGCCATGCAGTGGGTCCGGCAAGCTCCAGG
GAAGGGCCTGGAGTGGGTCTCAGGTATTAGCTGGAATAGTGGTAGCATAGCCTATGC
GGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGCTCCCTGTA
TCTGCTAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGC
GGGCACAGATTATTATGATAGTAGTGCTTCCGAACTTCCTGACTACTGGGGCCAGGG
AACCCTGGTCACCGTCTCCTCAG

Figure 9B-24: SEQ ID #24
GAGCTCCAGATGACCCAGTCTCCATCCTTCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCCAGTCAGGGCATTAGCAGTTATTTAGCCTGGTATCAGCAA
AAACCGGGGAAAGCCCCTAAACTCCTGATCTATGGTGCATCTACTTTGCAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACCATCAGC
AGCCTGCAGCCTGATGATTTTGCAACTTATTACTGCCAACAGTATAATAGTTATCCGT
GGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCAGC
TGCAGGAGTCGGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTG
CAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAG
GGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGCCTATG
CGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGT
ATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTCTATTACTGTGCGAAAG
TGGGCGGGGATACCTATGATATTACAAGTGGGGCGGATTACTTCGATCTCTGGGGCC
GTGGCGCCCTGGTCACTGTCTCCTCAG

Figure 9B-25: SEQ ID #25
GAGCTCGTGATGACCCAGTCTCCAGCCACCCTGTCTGTGTCTCCAGGGGAAAGAGCC
ACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAACTTAGCCTGGTACCAGCAG
AAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCATCCACCAGGGCCACTGGT
ATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGAGTTCACTCTCACCATCAGC
AGCCTGCAGTCTGAAGATTTTGCAGTTTATTACTGTCAGCAGTATAATAACTGGCCCT
CGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA**GGTGGTTCCTCTAGA**
TCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGGTGCA
GCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTG
TGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCA
GGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGCCTAT
GCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTG
TATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTCTATTACTGTGCGAAA
GTGGGCGGGGATACCTATGATATTACAAGTGGGGCGGATTACTTCGATCTCTGGGGC
CGTGGCGCCCTGGTCACTGTCTCCTCAG

Figure 9B-26: SEQ ID #26
GAGCTCGTGGTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTCACC
ATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGTTATGATGTACACTGGTAC
CAGCAGCTTCCAGGAACAGCCCCCAAACTCCTCATTTATGGTAACAAAAATCGGCCC
TCAGGGGTCCCTGACCGGTTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA
TCACTGGGCTCCGGGCTGAGGATGAGGCTGATTACTACTGCCAGTCCTTCGACAGCA
GCCTGGGGTGGGTGTTCGGCGGAGGGACCCAGCTGACCGTCCTCGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGA
GTCTCCTGCGCAGCCTCTGGATTCACCTCTAATATCTTTTGGATGAGTTGGGTCCGCC
AGGCTCCAGGTAAGGGGCTGGAGTGGGTGGCCAACATAGACGAAGATGGAAGTGAG
AAAAACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAG
AACTCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTAC
TGTGCGAGGGAGTCGTTTTACTATGGTTCGGGGACTTATTTTGACTTCTGGGGCCAGG
GAACCCTGGTCACCGTCTCCTCAG

Figure 9B-27: SEQ ID #27
GAGCTCGTGCTGACTCAGCCACCCTCGGTGCCAGTGGCCCCAGGACAGACGGCCAAC
ATTAGCTGTGGGGGAAACAACATTGGAAGACAGACTGTCCACTGGTACCAGCAGAA
GCCAGGCCAGGCCCCTGTGTTGGTCGTCTTTGATGATAGCGACCGGCCCGCAGGGAT
CCCTGAGCGATTCTCTGGCTCCAACTCTGGGAACACGGCCACCCTGACCATCAGCAG
GGTCGAAGCCGGGGATGAGGCCGACTATTACTGTCAGGTGTGGGATAGTAGTAGTG
ATCATGTGGTCTTCGGCGGAGGCACCCAGCTGACCGTCCTCGGC**GGTGGTTCCTC**
TAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAG
GTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGTCTGGGAGGTCCCTGAGACTC
TCCTGTGCAGCCTCTGGATTCACGTTCAGTGACTATGCCATGCACTGGGTCCGCCAGG
CCCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCACATGGTGGAACCAAAAAA
TACACCGGAGACTCCGTGAAGGGCCGATTTATCATCTCCAGAGACAATTCCAAGAAC
ACAGTGTTTTTGCAAATGAACAGCCTGAGAGTTGAGGACACGGCTGTTTATTACTGT
GCGAGAGATCGTGTAGAAGGTTACGTTTGGGGGGGCACGTTTGACCACTGGGGCCA
GGGAACCCCGGTCACCGTCTCCTCAG

Figure 9B-28: SEQ ID #28
GAGCTCGTGCTGACTCAGCCACCTTCAGTGGCCGTGTCCCCAGGACAGACAGCCAGC
ATCACCTGCTCTGGAGATAAATTGGGGGATAAATATGTTTCCTGGTATCAGCAGAAG
CCAGGCCAGTCCCCTGTTCTGGTCATGTATCGAGATACCAAGCGGCCCTCAGGGATC
CCTGAGCGATTTTCTGGCTCCAACTCCGGGAACACAGCCACTCTGACCATCAGCGGG
ACCCAGGCTATGGATGAGGCTGACTATTACTGTCAGGCGTGGGACAGCAACACTGGG
GTGTTCGGCGGAGGCACCAAGCTGACCGTCCTAGGC**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGC
TGTTGGAGTCTGGCCCAGGGCTGGAAAAGGTTTCGGAGACCCTGTCCCTCACGTGTA
ATGTCTCTGGTGTCTCCATAAGTAGTCCTGATTATTATTGGGCCTGGATCCGCCAGCC
CCCCGGGAAGGGGCTGGAGTGGATTGGCAGTATCTTTTACAGTGGACCTACCTCCTG
GAATCCGTCCCTCAAGAATCGAGTCACCATCTCAGTAGACACGTCCAAGAATCAATT
CTCCCTGAAAATGAAGTCTGTGACGGCCGCGGACACGGCCGTATATTACTGTGCGAG
GTCCTTCGGTTTCGGGAGATATGAGCCCGCGGATGATGCATTTGATATCTGGGGCCG
AGGGAGACTGGTCATCGTCTCTCCAG

Figure 9B-29: SEQ ID #29
GAGCTCGAGCTGACTCAGCCACCCTCAGTGTCAGTGGCCCTGGGACAGACGGCCAGG
ATTACCTGTGGGGGAAACAACATTGGAAGTAAAAATGTGCACTGGTACCAGCAGAA
GCCAGGCCAGGCCCCTGTGCTGGTCATCTATAGGGATAGCAACCGGCCCTCTGGGAT
CCCTGAGCGATTCTCTGGCTCCAACTCGGGGAACACGGCCACCCTGACCATCAGCAG
AGCCCAAGCCGGGGATGAGGCTGACTATTACTGTCAGGCGTGGGACAGAAGCACTG
CTCATGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTAGGT**GGTGGTTCCT**
CTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCA
GGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGACT
CTCCTGTACAGCCTCTAGATTCAATTTCAGGAGTTTTGCCATGCACTGGGTCCGCCAG
GCTCCAGGCAAGGGGCTGGAGTGGGTGGCGATGTTTCCTTATGACGGAAATAATACA
TACTATGGAGACTCCGTGAAGGGCCGATTCACCATCTCCAGAGACAATTCCAAGAAG
ATGCTGTACCTGCAAATGAACGATCTCAGAATTGACGACACGGCACTGTACTACTGT
GCGAGGCAGGGATGGGTAATAGAGACATCTGGTATAAGAGCGAGTGGCTTTGACGT
CTGGGGTCAAGGGACACTGGTCACCGTCTCCTCAG

Figure 9B-30: SEQ ID #30
GAGCTCGTGCTGACGCAGCCGCCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCGTCA
GTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCC
TGAATGGTCCGGTATTCGGCGGAGGCACCCAGCTGACCGTCCTCGGT**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAG
ACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGG
CAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGGAC
CATAGGCTACGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAA
GAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTGTATTA
CTGTGCAAAAGATGGGATTACGGTTTTTGGAGTGGGCGATGGTTTGGATATCTGGGG
CCAAGGGACAATGGTCACCGTCTCTTCAG

Figure 9B-31: SEQ ID #31
GAGCTCGTGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGACAGAGTC
ATCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGCAGTTATTTAGCCTGGTATCAG
CAAAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATTCACTTTACAAAGT
GGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAATC
AGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTTCTGTCAAGACCTTAGTGGTTATC
CTCGAAACACCTTCGGCCAAGGGACACGACTGGAGATTAAA**GGTGGTTCCTCTA**
GATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGT
GCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTC
CTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCT
CCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGCATAGA
CTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTC
CCTGTATCTGCAAATGAACAGTCTGAGAGTTGAGGACACGGCCTTGTATTATTGTGC
AAAAGATGGGAGTAGGGTTTTTGGAGTGGGCGGTGGTTTTGATTTCTGGGGCCAAGG
GACAATGGTCACCGTCTCTTCAG

Figure 9B-32: SEQ ID #32
GAGCTCGTGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCAGGCGAGTCAGGACATCAGGAAGTATTTAAATTGGTATCAGCAG
AAAGCAGGGAAAGCCCCTAAACTCCTGATCTACGATGCATCTAAGTTGGATATAGGG
CTCCCATCAAGGTTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCACCATCAGC
AGCCTGCAGCCTGAAGATATTGCAACATATTACTGTCAGCAGTTTGATAATCTCCCCT
TCACTTTCGGCGGAGGGACCAAGGTGGAAATCAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGC
TGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTG
CAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAG
GGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGGACCATAGGCTATG
CGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGT
ATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCAAAAG
ATGGGATTACGGTTTTTGGAGTGGGCGATGGTTTGGATATCTGGGGCCAAGGGACAA
TGGTCACCGTCTCTTCAG

Figure 9B-33: SEQ ID #33
GAGCTCATGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGGAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCGGTCCGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCC
TGAGTGGTTGGGTGTTCGGCGGAGGCACCCAGCTGACCGTCCTCGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
GAGGTGCAGCTGGTGGAGTCTGGAGGAGGCTTGGTCCAGCCTGGGGGGTCCGTGAG
ACTCTCCTGTGCAGCCTCTGGATTTCAAGTCAGTAGTGACCACATGAGCTGGGTCCG
CCAGGCTCCAGGGAAGGGACTGCAGTGGGTCTCAGTTATTTATACTGGGGGCAACTC
ATACTACGCAGACTCCGTGAAGGGCCGATTCACCGTCTCCAGAGACAACTCCAGGAA
CACACTTTTTCTTCAAATGAACAGCCTGAGAGTCGAGGACACGGCCATTTATTATTGT
GTGAGAGGTCCCGCTTACTATGACATAGACTACTGGGGCCAGGGAGCCCTGGTCACC
GTGTCCTCGG

Figure 9B-34: SEQ ID #34
GAGCTCGTGTTGACGCAGCCGCCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCC
TGAATGGTGGGGTGTTCGGCGGAGGCACCGAGCTGACCGTCCTCGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAG
ACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGG
CAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGGGC
CATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAA
GAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTGTATTA
CTGTGCAAAAGATGGGATTACGGTTTTTGGAGTGGGCGATGGTTTGGATATCTGGGG
CCAAGGGACAATGGTCACCGTCTCTTCAG

Figure 9B-35: SEQ ID #35
GAGCTCGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAACATGGGATGACAGCC
TGAATGGTCGGGTGTTCGGCGGAGGCACCCAGCTGACCGTCCTCGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
CAGGTGCAGCTGGTGCAGTCTGGGGGAGACTTGGTCCAGCCGGGGGGGTCCCTGAG
ACTCTCCTGTGTAGCCTCTGGATTCAACGTCAATGACAACTACATGAGCTGGGTCCG
CCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACGATTTACAGCGAAACTCTTTC
ATACTACGGAGACTCCGTGAAGGGCAGATTCACCGTCTCCAGAGACGGTTCCAAGAA
CACGGTGTTTCTTCAAATGAGCAGCCTGAAAGGCGAGGACACGGCTGTTTATTATTG
TGCTTCCGAAGGGGGGGGCCTGACAATTGACTATTGGGGCCAGGGAACCCTGGTCGC
CGTCTCCTCAG

Figure 9B-36: SEQ ID #36
GAGCTCGTGGTGACGCAGCCGCCCTCTGCATCTGCTGCCCTGGGATCCTCGGCCAAG
CTCACCTGCACCCTGAGCAGTGCCCACAAGACCTACACCATTGACTGGTATCAGCAG
CAGCAAGGGGAGGCCCCTCGGTACCTGATGCAACTTAAGAGTGATGGAAGCTACTCC
AAGGGGACCGGGGTCCCTGATCGCTTCTCGGGCTCCAGCTCTGGGGCTGACCGTTAC
TTGATCATCCCCAGCGTCCAGGCTGATGACGAAGCCGACTACTATTGTGGTGCAGAT
TATAGCGGTGGGTATTATGTGTTCGGCGGAGGCACCAAGCTGACCGTCCTAGGC**GG**
TGGTTCCTCTAGATCTTCCCCCTCTGGTGGCGGTGGCTCGGGCGGT
GGTGGGGAGGTGCAGCTGGTGGAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCC
TCAGTGAAGGTCTCCTGCAAGGCTTCTACATACATGTTCACCAGTTATGATATCAACT
GGGTGCGACAGGCCGCTGGACAAGGGCTTGAGTGGATGGGATGGATGGACCCGAAT
ACTGGTAACACAGACTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACCAGGAA
CACTTCCATAAATACAGCCTACATGGAGCTGAGAAGCCTGACGTCTGACGACACGGC
CGTATATTACTGTGCGAGAGGCCGGACAGTGCGGTTCGGGGAATTATTTGTTAGTGA
GGGGGGTATGGACGTCTGGGGCCAAGGGACCACGGTCAGCGTCTCCTCAG

Figure 9B-37: SEQ ID #37
GAGCTCGTGATGACTCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTGGGCTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAACTCCTGATCTATGCTGCATCCAATTTACAAAGTGGG
GTCCCATCAAGGTTCAGCGGCAGTGGATCTGGCACAGATTTCACTCTCACCATCAGC
AGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAAGATTACAATTACCCGC
TCACTTTCGGCGGAGGGACCAAGCTGGAGATCAAA**GGTGGTTCCTCTAGATCT**
TCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGCT
GGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGC
AGCCTCTGGATTCACCTTTGATGATCATGCCATGCACTGGGTCCGGCAAGCTCCAGG
GAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAGTGGTGCTTACATAGCCTATGC
GGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAGGAACTCCCTGTA
TCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCCCGCAG
TAGTGGTTATTATGACCTTCCCTATGCTTTTGATATCTGGGGCCAAGGGACAATGGTC
ACCGTCTCTTCAG

Figure 9B-38: SEQ ID #38
GAGCTCGTGCTGACTCAATCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTCACC
ATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGTTATGATGTACACTGGTAC
CAGCAGCTTCCAGGAACAGCCCCCAAACTCCTCATCTATGATAACAGCAATCGGCCC
TCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA
TCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCTATGACAGCA
GCCTGAGTGCCTGGGTGTTCGGCGGAGGGACCAAGGTGACCGTCCTAGGC**GGTGG**
TTCCTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGT
GGGGAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCT
GAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTC
CGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGT
AGCATAGACTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCC
AAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGTTGAGGACACGGCCTTGTAT
TATTGTGCAAAAGATGGGAGTAGGGTTTTTGGAGTGGGCGGTGGTTTTGATTTCTGG
GGCCAAGGGACAATGGTCACCGTCTCTTCAG

Figure 9B-39: SEQ ID #39
GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGG
GTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCC
ACCTTCGGCCAAGGGACACGACTGGAGATTAAA**GGTGGTTCCTCTAGATCTT**
CCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGGAGGTGCAGCTGG
TGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAG
CCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGA
AGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGGACCATAGGCTATGCGG
ACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATC
TGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCAAAAGAT
GGGATTACGGTTTTTGGAGTGGGCGATGGTTTGGATATCTGGGGCCAAGGGACAATG
GTCACCGTCTCTTCAG

Figure 9B-40: SEQ ID #40
GAGCTCGAGCTGACTCAGCCACCCTCAGTGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAGGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCC
TGAATGGTGTGGTGTTCGGCGGAGGGACCAAGGTGACCGTCCTAGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
CAGGTGCAGCTGCAGGAGTCGGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAG
ACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGG
CAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGC
ATAGCCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAG
AACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTCTATTAC
TGTGCGAAAGTGGGCGGGGATACCTATGATATTACAAGTGGGGCGGATTACTTCGAT
CTCTGGGGCCGTAGCGCCCTGGTCACTGTCTCCTCAG

Figure 9B-41: SEQ ID #41
GAGCTCGAGCTGACTCAGCCACCCTCAGTGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCAGTCTGAGGATGAGGCTGATTATTTCTGTGCAGCATGGGATGACAGCC
TGAATGGCCTCGTTTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGC**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAG
ACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGG
CAAGGTCCAGGGAAGGGCCTAGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGGAC
CATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAA
GAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTGTATTA
CTGTGCAAAAGATGGGATTACGGTTTTTGGAGTGGGCGATGGTTTGGATATCTGGGG
CCAAGGGACAATGGTCACCGTCTCTTCAG

Figure 9B-42: SEQ ID #42
GAGCTCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTC
ACCATCACTTGCCGGGCAAGTCAGAGCATTAGCACCTATTTAAATTGGTATCAGCAG
AAACCAGGGAAAGCCCCTATGCTCCTGATCTACGCTGCATCCAATTTGCAAAGTGGG
GTCCCATCAAGGTTCAGTGGCAGTGGGTCTGGGACAGATTTCACTCTCACCATCAGC
AGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCG
ATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA**GGTGGTTCCTCTAGATC**
TTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGGCAGATCACCTT
GAAGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGCGACTCTCCTGTGC
AGCCTCTGGATTCGACTTCAATATCTATGGCATGCACTGGGTCCGCCAGGCTCCAGA
CAAGGGGCTGGAGTGGGTGGCGGTTATATCAGATGATGGAACTAAAAAATATTATG
CAGACTCTGTGAAGGGCCGAGTCACCATCTCCAGAGACAATTCCAAGAACACGCTGT
ATCTGCAGATGAACAGCCTGAGAGCTGAGGACACGGCTGTGTATTACTGTGCGAAAG
ATCTGGATGTTGTCATGGGACCCGGTGGACTTGATTATTGGGGCCAGGGAACCCTGG
TCACCGTCTCCTCAG

Figure 9B-43: SEQ ID #43
GAGCTCGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACC
ATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATACTGTAAACTGGTACCAG
CAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCA
GGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCA
GTGGGCTCCAGTCTGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCC
TGAATGGTCGGGTGTTCGGCGGAGGCACCAAGCTGACCGTCCTAGGT**GGTGGTTC**
CTCTAGATCTTCCTCCTCTGGTGGCGGTGGCTCGGGCGGTGGTGGG
CAGATCACCTTGAAGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGC
AAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGGACC
ATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAG
AACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTGTATTAC
TGTGCAAAAGATGGGATTACGGTTTTTGGAGTGGGCGATGGTTTGGATATCTGGGGC
CAAGGGACAATGGTCACCGTCTCTTCAG

Figure 9B-44: SEQ ID #44
ELVLTQSPDSLSVSLGERATINCKSSQTVLYNSDNKNYLSWYQQKPGQPPKLIMNWASIR
ASGVPDRFSGSGSGTDFTLTINSLQAEDVAIYYCQQYYSTPLTFGGGTKVEIK**GGSSRSS**
SSGGGGSGGGGQVQLVQSGAEVKKPGALVKVSCKASGYTFTNYGITWVRQAPGQG
LEWMGWISVYNGDTKYAQKLQGRVTMTTDTPTNTVYMELRSLRSDDTAVYYCARGYG
SGNWDYWGQGTLVTVSS

Figure 9B-45: SEQ ID #45
ELTLTQSPSSLSASVGDRVTITCRASQGIASYLAWYQQKPGKAPKLLIYGASTLQSGVPSR
FSGRRSGTDFTLTISSLQPEDAATYYCQQYSNYPLTFGQGTKLEIK**GGSSRSSSSGGG**
GSGGGGQVQLVQSGAEMKKPGASVKVSCKASGYTFTNYGITWVRQAPGQGLEWMG
WISVYNGDTKYAQKLQGRVTMTTDTPTSTVYMELRSLTSDDTAVYYCVRGYGSGNWD
YWGQGTLVTVSS

Figure 9B-46: SEQ ID #46
ELQMTQSPSSLSASVGDRVTITCRASQGINNYLAWFQQKPGKAPKLLIYKASSLESGVPS
RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPFTFGPGTKVDIK**GGSSRSSSSGGG**
GSGGGGQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGITWVRQAPGQGLEWMG
WISVYNGDTKYAQKLQGRVTMTTDTPTNTVYMELRSLRSDDTAVYYCARGYGSGNWD
YWGQGTLVTVSS

Figure 9B-47: SEQ ID #47
ELQMTQSPSTLSASVGDRVTITCRASQGISNWLAWYQQKPGKAPKLLIHKASSLESGVPS
RFSGSGSGTEFTLTISSLQPDDFATYYCQQYYTYPLTFGGGTKVEIK**GGSSRSSSSGGG**
GSGGGGQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGITWVRQAPGQGLEWMG
WISVYNGDTKYAQKLQGRVTMTTDTPTNTVYMELRSLRSDDTAVYYCARGYGSGNWD
YWGQGTLVTVSS

Figure 9B-48: SEQ ID #48
ELVLTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIKGASTRATGIPD
RFSGSGSGTDFTLTISSLQAEDVAVYYCHQYYGPYSFGQGTKVEIK**GGSSRSSSSGGG**
GSGGGGQVQLVQSGAEVKKPGSSVKVSCKASGYTFTNYGITWVRQAPGQGLEWMG
WISVYNGDTKYAQKLQGRVTMTTDTPTNTVYMELRSLRSDDTAVYYCARGYGSGNWD
YWGQGTLVTVSS

Figure 9B-49: SEQ ID #49
ELQMTQSPSSLSASVGDRVTITCRATQGISNYLAWFQQKPGKAPKLLIYAASSLQSGVPS
KFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKVEIK**GGSSRSSSSGGG**
GSGGGGQVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGITWVRQAPGQGLEWMG
WISVYNGDTKYAQKLQGRVTMTTDTLTNTVYMELRSLRSDDTAVYYCARGYGSGNWD
YWGQGTPVTVSS

Figure 9B-50: SEQ ID #50
ELQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPRTFGGGTKLEIK**GGSSRSSSSGGGG**
SGGGGQVQLVQSGAEVRKPGASVRVSCKASGYTLTTYDINWVRQATGQGLEWMGW
MNPTSGNTAYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCARGLFFGVVTKPN
YYYYAMDVWGQGTTVTVSS

Figure 9B-51: SEQ ID #51
ELQMTQSPSSLSVSVGDRVTITCRASQSISGYLNWYQQKPGKAPKLLIYGASSLQSGVPS
RFSGSGSGTDFALTISSVQPEDFASYFCQQSHSVPINFGQGTRLEIK**GGSSRSSSSGGG**
GSGGGGQVQLVQSGGGLAQPGKSLRLSCVASGFTFDDYAMHWVRQAPGKGLEWVS
GINWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEQGYCDSTGC
QRGSGMDVWGQGTTVTVSS

Figure 9B-52: SEQ ID #52
ELQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPS
RLSGSGSGTDFTFTISSLQPEDIATYYCQQYDDLPLTFGGGTKLEIK**GGSSRSSSSGGG**
GSGGGGQVQLVQSGGGLAQPGKSLRLSCVASGFTFDDYAMHWVRQAPGKGLEWVS
GINWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEQGYCDSTGC
QRGSGMDVWGQGTTVTVSS

Figure 9B-53: SEQ ID #53
ELQMTQSPSSLAASVGDRVTITCRASHDIKNDLGWYQHQPGKAPKLLIYAASSLQSGVPS
RFSGSGSGTNFTLTINSLQPEDFATYYCLHDYTYPRTFGQGTKVEIK**GGSSRSSSSGG**
GGSGGGGQVQLVQSGGGLAQPGKSLRLSCVASGFTFDDYAMHWVRQAPGKGLEWV
SGINWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEQGYCDSTG
CQRGSGMDVWGQGTTVTVSS

Figure 9B-54: SEQ ID #54
ELQMTQSPSSLSASVGDRVTITCRASQGIRYDVGWYQQKPGKAPKLLIYAASTLQSGVPS
RFSGSGSETDFTLTINSLQPEDSATYYCQQSYSIPSTFGQGTKVEIK**GGSSRSSSSGGG**
GSGGGGEVQLLESGGGLAQPGKSLRLSCVASGFTFDDYAMHWVRQAPGKGLEWVSG
INWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEQGYCDSTGCQ
RGSGMDVWGQGTTVTVSS

Figure 9B-55: SEQ ID #55
ELELTQPPSVSGTPGQRVTISCSGSSSNIGSDTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYYCATWDDGLRGMVFGEGTKLTVLG**GGSSRSSS**
SGGGGSGGGGQVQLQESGGGLAQPGKSLRLSCVASGFTFDDYAMHWVRQAPGKGL
EWVSGINWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEQGYC
DSTGCQRGSGMDVWGQGTTVTVSS

Figure 9B-56: SEQ ID #56
ELVLTQPPSVSGAPGRRVTISCTGSSSNIGAAYDVHWYQQLPGTAPKLLIFGNTNRPSGVP
DRFSGSKSGTSASLAITGLQSEDEADYYCATWDDSRDGPEVVFGGGTELTVLG**GGSSR**
SSSSGGGGSGGGGEVQLVESGGGLAQPGKSLRLSCVASGFTFDDYAMHWVRQAPG
KGLEWVSGINWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEQ
GYCDSTGCQRGSGMDVWGQGTTVTVSS

Figure 9B-57: SEQ ID #57
ELVLTQPPSASGTPGQRVTISCSGSNSNIGSDYVYWYQRFPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEAEYYCATWDDALRGMVFGEGTKLTVLG**GGSSRSSS**
SGGGGSGGGGEVQLVESGGGLAQPGKSLRLSCVASGFTFDDYAMHWVRQAPGKGL
EWVSGINWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEQGYC
DSTGCQRGSGMDVWGQGTTVTVSS

Figure 9B-58: SEQ ID #58
ELMLTQPHSVSESPGKTVTISCTRSSGSIASNFVQWYQQRPGKSPTTVIYEDNQRPSGVPD
RFSGSVDRSSNSASLTISGLQTEDEADYYCQSFYDGVPSWVFGGGTELTVLG**GGSSRSS**
SSGGGGSGGGGEVQLVESGGGVVQPGGSLRLSCVASGFTFDDYAMHWVRQAPGKG
LEWVSGINWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEQGY
CDSTGCQRGSGMDVWGQGTTVTVSS

Figure 9B-59: SEQ ID # 59
ELMLTQPHSVSESPGKTVTISCTRSSGSIASNFVQWYQQRPGKSPTTVIYEDNQRPSGVPD
RFSGSVDRSSNSASLTISGLQTEDEADYYCQSFYDGVPSWVFGGGTELTVLG**GGSSRSS**
SSGGGGSGGGGQVQLVQSGGGVVQPGGSLRLSCVASGFTFDDYAMHWVRQAPGK
GLEWVSGISWNSGAIGYADSVKGRFTISRDNAKNSLYLQMNSLRTEDTAVYYCAKDGIT
IFGVGDGLDVWGQGTMVTVSS

Figure 9B-60: SEQ ID #60
ELQMTQSPSSLSASVGDRVTITCQASQDIGNYLNWYQQKPGKAPKLLIYDASYLETGVPS
RFSGSGSGTDFTFTISSLQPEDIATYYCQQYDNLPFTFGPGTKVDIK**GGSSRSSSSGGG**
GSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG
ISWNSGSIDYADSVKGRFTISRDNAKNSLYLQMNSLRVEDTALYYCAKDGSRVFGVGGG
FDFWGQGTMVTVSS

Figure 9B-61: SEQ ID #61
ELVMTQSPSSLSASVGDRVTITCRASQGITDDLGWYQQKPGKAPKLLIYATSNLESGVPS
RFSGSGSDTEFTLTISSLQPEDLATYYCLQDYSYPYTFGQGTKVEIK**GGSSRSSSSGGG**
GSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG
ISWNSGSIDYVDSVKGRFTISRDNAKNYLYLQMNSLRVEDTALYYCAKDGSRVFGVGG
GFDFWGQGTMVTVSS

Figure 9B-62: SEQ ID #62
ELQMTQSPSTLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYKASSLESGVPS
RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNTYSRTFGQGTKVEIK**GGSSRSSSSGGG**
GSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSG
ISWNSGGIGYADSVRGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDGMRVFGVGG
GFDFWGQGTMVTVSS

Figure 9B-63: SEQ ID #63
ELQMTQSPSSLSASVGDRVTITCQASRDISNYLNWYQHIPGKAPKLLIFHASTLEAGIPSRF
SGSGSETSFTFTIRSLQPEDVATYYCQQYDNLPFTFGPGTKVDIK**GGSSRSSSSGGGG**
SGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMYWVRQAPGKGLEWVSGIS
WNSGSIDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDGMRVFGVGGGF
DFWGQGTMVTVSS

Figure 9B-64: SEQ ID #64
ELMLTQPHSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGPVFGGGTKVTVLG**GGSSRSSS**
SGGGGSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMYWVRQAPGKGL
EWVSGISWNSGSIDYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDGMRV
FGVGGGFDFWGQGTMVTVSS

Figure 9B-65: SEQ ID #65
ELVVTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYYCATWDDGLNGMVFGGGTKLTVLG**GGSSRSSS**
SGGGGSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGL
EWVSGISWNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDGITVF
GVGDGLDIWGQGTMVTVSS

Figure 9B-66: SEQ ID #66
ELQMTQSPSSLSASVGDRVTITCRASQGIGNDLGWYQQKPGKAPKLLIYAASSLQSGVPS
RFSGSGSGTDFTLTIGSLQPEDFATYYCLQDYNYPFTFGPGTKVDIK**GGSSRSSSSGGG**
GSGGGGEVQLVESGGTLVQPGRSLRLSCAASGFSFDDYAMQWVRQAPGKGLEWVSG
ISWNSGSIAYADSVKGRFTISRDNAKSSLYLLMNSLRAEDTALYYCAKAGTDYYDSSASE
LPDYWGQGTLVTVSS

Figure 9B-67: SEQ ID #67
ELQMTQSPSFLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYGASTLQSGVPS
RFSGSGSGTEFTLTISSLQPDDFATYYCQQYNSYPWTFGQ
GTKVEIK**GGSSRSSSSGGGGSGGGG**QVQLQESGGGLVQPGRSLRLSCAASGFTFD
DYAMHWVRQAPGKGLEWVSGISWNSGSIAYADSVKGRFTISRDNAKNSLYLQMNSLRA
EDTAFYYCAKVGGDTYDITSGADYFDLWGRGALVTVSS

Figure 9B-68: SEQ ID #68
ELVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPA
RFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPSITFGQGTRLEIK**GGSSRSSSSGG**
GGSGGGGQVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV
SGISWNSGSIAYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAFYYCAKVGGDTYDITS
GADYFDLWGRGALVTVSS

Figure 9B-69: SEQ ID #69
ELVVTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNKNRPSGV
PDRFSGSKSGTSASLAITGLRAEDEADYYCQSFDSSLGWVFGGGTQLTVLG**GGSSRSSS**
SGGGGSGGGGQVQLVQSGGGLVQPGGSLRVSCAASGFTSNIFWMSWVRQAPGKGL
EWVANIDEDGSEKNYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARESFYY
GSGTYFDFWGQGTLVTVSS

Figure 9B-70: SEQ ID #70
ELVLTQPPSVPVAPGQTANISCGGNNIGRQTVHWYQQKPGQAPVLVVFDDSDRPAGIPE
RFSGSNSGNTATLTISRVEAGDEADYYCQVWDSSSDHVVFGGGTQLTVLG**GGSSRSSS**
SGGGGSGGGGQVQLVQSGGGVVQSGRSLRLSCAASGFTFSDYAMHWVRQAPGKGL
EWVAVISHGGTKKYTGDSVKGRFIISRDNSKNTVFLQMNSLRVEDTAVYYCARDRVEG
YVWGGTFDHWGQGTPVTVSS

Figure 9B-71: SEQ ID #71
ELVLTQPPSVAVSPGQTASITCSGDKLGDKYVSWYQQKPGQSPVLVMYRDTKRPSGIPE
RFSGSNSGNTATLTISGTQAMDEADYYCQAWDSNTGVFGGGTKLTVLG**GGSSRSSSS**
GGGGSGGGGEVQLLESGPGLEKVSETLSLTCNVSGVSISSPDYYWAWIRQPPGKGLE
WIGSIFYSGPTSWNPSLKNRVTISVDTSKNQFSLKMKSVTAADTAVYYCARSFGFGRYEP
ADDAFDIWGRGRLVIVSP

Figure 9B-72: SEQ ID #72
ELELTQPPSVSVALGQTARITCGGNNIGSKNVHWYQQKPGQAPVLVIYRDSNRPSGIPER
FSGSNSGNTATLTISRAQAGDEADYYCQAWDRSTAHVVFGGGTKLTVLG**GGSSRSSS**
SGGGGSGGGGQVQLVQSGGGVVQPGRSLRLSCTASRFNFRSFAMHWVRQAPGKGL
EWVAMFPYDGNNTYYGDSVKGRFTISRDNSKKMLYLQMNDLRIDDTALYYCARQGWV
IETSGIRASGFDVWGQGTLVTVSS

Figure 9B-73: SEQ ID #73
ELVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAVSGLQSEDEADYYCAAWDDSLNGPVFGGGTQLTVLG**GGSSRSSS**
SGGGGSGGGGQVQLQESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGL
EWVSGISWNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDGITVF
GVGDGLDIWGQGTMVTVSS

Figure 9B-74: SEQ ID #74
ELVMTQSPSSVSASVGDRVIITCRASQGISSSYLAWYQQKPGKAPKLLIYAAFTLQSGVPS
RFSGSGSGTEFTLTISSLQPEDFATYFCQDLSGYPRNTFGQGTRLEIK**GGSSRSSSSGG**
GGSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWV
SGISWNSGSIDYADSVKGRFTISRDNAKNSLYLQMNSLRVEDTALYYCAKDGSRVFGVG
GGFDFWGQGTMVTVSS

Figure 9B-75: SEQ ID #75
ELVMTQSPSSLSASVGDRVTITCQASQDIRKYLNWYQQKAGKAPKLLIYDASKLDIGLPS
RFSGSGSGTDFTFTISSLQPEDIATYYCQQFDNLPFTFGGGTKVEIK**GGSSRSSSSGGG**
GSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG
ISWNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDGITVFGVGDG
LDIWGQGTMVTVSS

Figure 9B-76: SEQ ID #76
ELMLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYRNNQRPSGVPD
RFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSGWVFGGGTQLTVLG**GGSSRSSS**
SGGGGSGGGGEVQLVESGGGLVQPGGSVRLSCAASGFQVSSDHMSWVRQAPGKGL
QWVSVIYTGGNSYYADSVKGRFTVSRDNSRNTLFLQMNSLRVEDTAIYYCVRGPAYYDI
DYWGQGALVTVSS

Figure 9B-77: SEQ ID #77
ELVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGGVFGGGTELTVLG**GGSSRSSS**
SGGGGSGGGGQVQLQESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGL
EWVSGISWNSGAIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDGITVF
GVGDGLDIWGQGTMVTVSS

Figure 9B-78: SEQ ID #78
ELVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYYCATWDDSLNGRVFGGGTQLTVLG**GGSSRSSS**
SGGGGSGGGGQVQLVQSGGDLVQPGGSLRLSCVASGFNVNDNYMSWVRQAPGKG
LEWVSTIYSETLSYYGDSVKGRFTVSRDGSKNTVFLQMSSLKGEDTAVYYCASEGGGLT
IDYWGQGTLVAVSS

Figure 9B-79: SEQ ID #79
ELVVTQPPSASAALGSSAKLTCTLSSAHKTYTIDWYQQQQGEAPRYLMQLKSDGSYSKG
TGVPDRFSGSSSGADRYLIIPSVQADDEADYYCGADYSGGYYVFGGGTKLTVLG**GGSS**
RSSPSGGGGSGGGGEVQLVESGAEVKKPGASVKVSCKASTYMFTSYDINWVRQAA
GQGLEWMGWMDPNTGNTDYAQKFQGRVTMTRNTSINTAYMELRSLTSDDTAVYYCA
RGRTVRFGELFVSEGGMDVWGQGTTVSVSS

Figure 9B-80: SEQ ID #80
ELVMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKLLIYAASNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCLQDYNYPLTFGGGTKLEIK**GGSSRSSSSGGG**
GSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDHAMHWVRQAPGKGLEWVSG
ISWSGAYIAYADSVKGRFTISRDNARNSLYLQMNSLRAEDTALYYCARSSGYYDLPYAF
DIWGQGTMVTVSS

Figure 9B-81: SEQ ID #81
ELVLTQSPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNSNRPSGV
PDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSAWVFGGGTKVTVLG**GGSSRS**
SSSGGGGSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGK
GLEWVSGISWNSGSIDYADSVKGRFTISRDNAKNSLYLQMNSLRVEDTALYYCAKDGSR
VFGVGGGFDFWGQGTMVTVSS

Figure 9B-82: SEQ ID #82
ELQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSR
FSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPTFGQGTRLEIK**GGSSRSSSSGGGGS**
GGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGIS
WNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDGITVFGVGDGL
DIWGQGTMVTVSS

Figure 9B-83: SEQ ID #83
ELELTQPPSVSGTPGQRVTISCSGGSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGVVFGGGTKVTVLG**GGSSRSSS**
SGGGGSGGGGQVQLQESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGL
EWVSGISWNSGSIAYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAFYYCAKVGGDT
YDITSGADYFDLWGRSALVTVSS

Figure 9B-84: SEQ ID #84
ELELTQPPSVSGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYFCAAWDDSLNGLVFGGGTKLTVLG**GGSSRSSS**
SGGGGSGGGGEVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQGPGKGL
EWVSGISWNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDGITVF
GVGDGLDIWGQGTMVTVSS

Figure 9B-85: SEQ ID #85
ELQMTQSPSSLSASVGDRVTITCRASQSISTYLNWYQQKPGKAPMLLIYAASNLQSGVPS
RFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPITFGQGTRLEIK**GGSSRSSSSGGG**
GSGGGGQITLKESGGGVVQPGRSLRLSCAASGFDFNIYGMHWVRQAPDKGLEWVAVI
SDDGTKKYYADSVKGRVTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDLDVVMGPGG
LDYWGQGTLVTVSS

Figure 9B-86: SEQ ID #86
ELVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYSNNQRPSGVPD
RFSGSKSGTSASLAISGLQSEDEADYYCAAWDDSLNGRVFGGGTKLTVLG**GGSSRSSS**
SGGGGSGGGGQITLKESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLE
WVSGISWNSGTIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAKDGITVFG
VGDGLDIWGQGTMVTVSS