Anti-IL 17A/IL-17F Cross-Reactive Antibodies and Methods of Use Thereof

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/126,465, filed May 5, 2008, and U.S. Provisional Application No. 61/098,369, filed September 19, 2008, the contents of each of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

This invention relates generally to the generation of monoclonal antibodies, *e.g.*, fully human monoclonal antibodies, that recognize IL-17F, to monoclonal antibodies, *e.g.*, fully human antibodies that recognize the heterodimeric IL-17A/IL-17F complex, and to monoclonal antibodies, *e.g.*, fully human cross-reactive antibodies that recognize both IL-17F and IL-17A when not complexed together, and to methods of using the monoclonal antibodies as therapeutics.

BACKGROUND OF THE INVENTION

IL-17A (originally named CTL-8, and also known as IL-17) is the archetypical/founding member of the IL-17 family of cytokines. In addition to IL-17A, members of the IL-17 cytokine family presently include the proteins IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25) and IL-17F that share a conserved C-terminal region but different N-terminal segments.

IL-17A and IL-17F are the two most closely related members of the family, both in terms of sequence and biological properties. IL-17F shares 55% sequence identity with IL-17A at the amino acid level. Both IL-17A and IL-17F are secreted as disulfide linked homodimers which signal through the receptors IL-17R, IL-17RC, or a multimeric receptor complex composed of the IL-17R and IL-17RC. Both are also co-expressed on the same T cell subsets (principally by the Th17 $CD4^+$ T cells).

Moreover, both have been similarly implicated as contributing agents to progression and pathology of a variety of inflammatory and auto-immune diseases in humans and in mouse models of human diseases. Specifically, IL-17A and IL-17F have been implicated as major effector cytokines that trigger inflammatory responses and thereby contribute to a number of autoinflammatory diseases including multiple sclerosis, rheumatoid arthritis, and inflammatory bowel diseases and cancer.

The demonstrated *in vivo* activities of both IL-17A and IL-17F illustrate the clinical and/or therapeutic potential of, and need for, IL-17A and IL-17F antagonists. Specifically, antibodies that bind to both IL-17A and IL-17F and inhibit (antagonist antibodies) one or more of the immunological activities of both IL-17A and Il-17F would be beneficial. Thus, there remains a need in the art for an antagonist to are cross reactive to both IL-17A and IL-17F and IL-17A/IL-17F heterodimeric complex.

SUMMARY OF THE INVENTION

The present invention provides monoclonal antibodies such as fully human monoclonal antibodies which specifically bind to IL-17F, the IL-17F homodimer, IL-17A, the IL-17A homodimer and/or the heterodimeric IL-17A/IL-17F complex. The antibodies of the invention are capable of modulating, *e.g.*, blocking, inhibiting, reducing, antagonizing, neutralizing or otherwise interfering with IL-17, IL-17A and/or IL-17A/IL-17F mediated pro-inflammatory cytokine and/or chemokine production.

Exemplary monoclonal antibodies of the invention include, for example, the 30D12 antibody, the 29D8 antibody, the 1E4 antibody, the 31A3 antibody, the 39F12 antibody, the 12B12 antibody, the 15B7 antibody, the 4H11 antibody, 4B11 antibody, the 8B11 antibody, the 38B1 antibody, the 15E6 antibody, the 5E12 antibody, the 41B10 antibody, and variants thereof. Variants of such antibodies include the 30D12BF antibody (a variant of the 30D12 antibody having a modified heavy chain variable region), the 39F12A antibody (a variant of the 39F12 antibody having a modified heavy chain variable region), and the 15E6FK antibody (a variant of the 15E6 antibody having a modified light chain variable region). Alternatively, the monoclonal antibody is an antibody that binds to the same epitope as the 30D12 antibody, the 29D8 antibody, the 1E4 antibody, the 31A3 antibody, the 39F12 antibody, the 12B12 antibody, the 15B7 antibody, the 4H11 antibody, the 4B11 antibody, the 8B11 antibody, the 38B1 antibody, the 15E6 antibody, the 5E12 antibody, the 41B10 antibody, and variants thereof, including the 30D12BF antibody, the 39F12A antibody and the 15E6FK antibody. Each of these antibodies are respectively referred to herein as "huIL-17A/F" antibodies. The huIL-17A/F antibodies include fully human monoclonal antibodies, as well as humanized monoclonal antibodies and chimeric antibodies. Preferably, the antibodies are IgG_1.

These antibodies show specificity for human IL-17F, IL-17 A and/or the IL-17A/IL-17F heterodimeric complex, and they have been shown to inhibit IL-17F, IL-17A and/or IL-

17A/IL-17F mediated cytokine production. These antibodies have distinct specificities. In some embodiments the huIL-17A/F antibodies of the invention specifically binds both IL-17F and IL-17A alone (*i.e.*, when not complexed together). In some embodiments, the huIL-17A/F antibodies of the invention specifically bind IL-17F, the IL-17F homodimer, and the IL-17A/IL-17F heterodimeric complex. In some embodiments, the huIL-17A/F antibodies of the invention specifically binds IL-17F, the IL-17F homodimer, IL-17A, the IL-17A homodimer, and the IL-17A/IL-17F heterodimeric complex. For example, 30D12, 29D8, 1E4, 31A3, 39F12, 12B12, 15B7, 4H11, 38B1, 15E6, 30D12BF, 4B11, 15E6FK, and 39F12A bind IL-17F and cross-react with IL-17A, and these antibodies also bind the IL-17A/IL-17F heterodimeric complex. The 5E12 and 41B10 antibodies bind IL-17F and the IL-17F homodimer, but do not bind IL-17A or the IL-17A homodimer. The 41B10 antibody also binds the IL-17A/IL-17F heterodimeric complex.

The fully human antibodies of the invention contain a heavy chain variable region having the amino acid sequence of SEQ ID NOS: 2, 6, 8, 10, 14, 18, 20, 24, 28, 32, 34, 38, 44, 48, 52, and 54. The fully human antibodies of the invention contain a light chain variable region having the amino acid sequence of SEQ ID NOS: 4, 12, 16, 22, 26, 30, 36, 40, 46, and 56. The three heavy chain CDRs include a CDR1 region comprising an amino acid sequence at least 90%, 92%, 95%, 97% 98%, 99% or more identical to a sequence selected from the group consisting of SEQ ID NOS: 57, 60, 66, 69, 76, 79, 82, 85 and 90; a CDR2 region comprising an amino acid sequence at least 90%, 92%, 95%, 97% 98%, 99% or more identical to a sequence selected from the group consisting of SEQ ID NOs: 58, 61, 63, 65, 67, 70, 72, 74, 77, 80, 83, 86, 88, 91, 93 and 94; and a CDR3 region comprising an amino acid sequence at least 90%, 92%, 95%, 97% 98%, 99% or more identical to a sequence selected from the group consisting of SEQ ID NOs: 59, 62, 64, 68, 71, 73, 75, 78, 81, 84, 87, 89, 92, and 95. The three light chain CDRs include a CDR1 region comprising an amino acid sequence at least 90%, 92%, 95%, 97% 98%, 99% or more identical to a sequence selected from the group consisting of SEQ ID NOs: 96, 101, 104, 107 and 110; a CDR2 region comprising an amino acid sequence at least 90%, 92%, 95%, 97% 98%, 99% or more identical to a sequence selected from the group consisting of SEQ ID NOs: 97, 102, 105 and 108; and a CDR3 region comprising an amino acid sequence at least 90%, 92%, 95%, 97% 98%, 99% or more identical to a sequence selected from the group consisting of SEQ ID NOs: 98, 99, 100, 103, 106, 109, 111, 112 and 113.

Antibodies of the invention that specifically bind IL-17F, IL-17A and the IL-17A/IL-17F heterodimeric complex recognize and bind to an epitope that is shared by IL-

17F and IL-17A. Antibodies of the invention specifically bind the heterodimeric IL-17A/IL-17F complex, wherein the antibody binds to an epitope that includes one or more amino acid residues on human IL-17F, IL-17A or both. Antibodies of the invention immunospecifically bind IL-17F wherein the antibody binds to an epitope that includes one or more amino acid residues on human IL-17F. Antibodies of the invention specifically bind IL-17A wherein the antibody binds to an epitope that includes one or more amino acid residues on human IL-17F, IL-17A or both.

The huIL-17A/F antibodies bind to a common epitope that is found on both the IL-17F homodimer, the IL-17A homodimer and the IL-17A/IL-17F heterodimeric complex. Unlike antibodies that bind to an epitope at the interface or otherwise spans the IL-17A/IL-17F heterodimeric complex, the huIL-17A/F antibodies specifically bind the IL-17A/IL-17F heterodimeric complex and also recognize and bind IL-17F and IL-17A when not complexed together. Thus, the huIL-17A/F antibodies do not require the formation of the IL-17A/IL-17F complex to recognize IL-17F and/or IL-17A.

The huIL-17A/F antibodies exhibit a neutralizing ability and inhibit one or more biological functions of IL-17F, IL-17A and/or the IL-17A/IL-17F heterodimeric complex. The huIL-17A/F antibodies are able to bind each IL-17F including the IL-17F homodimer, IL-17A including the IL-17A homodimer, and the IL-17A/IL-17F heterodimeric complex.

The huIL-17A/IL-17F antibodies bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (i) a binding affinity of at least 100 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 300 pM or less against the IL-17F homodimer, (iii) a binding affinity of at least 400 pM or less against the IL-17A/IL-17F heterodimeric complex, (iv) a neutralizing ability of at least 13 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 120 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 31 nM or less against the IL-17A/IL-17F heterodimeric complex.

In some embodiments, the huIL-17A/IL-17F antibodies bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (i) a binding affinity of at least 40 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 10 pM or less against the IL-17F homodimer, and (iii) a binding affinity of at least 50 pM or less against the IL-17A/IL-17F heterodimer.

In some embodiments, the huIL-17A/IL-17F antibodies bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (i) a binding affinity of at least 15 pM or less against the IL-17A homodimer, (ii) a

binding affinity of at least 10 pM or less against the IL-17F homodimer, and (iii) a binding affinity of at least 30 pM or less against the IL-17A/IL-17F heterodimer.

In some embodiments, the huIL-17A/IL-17F antibodies bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (iv) a neutralizing ability of at least 13 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.9 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 11 nM or less against the IL-17A/IL-17F heterodimeric complex.

In some embodiments, the huIL-17A/IL-17F antibodies bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (iv) a neutralizing ability of at least 1.6 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.7 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 1.1 nM or less against the IL-17A/IL-17F heterodimeric complex.

In some embodiments, the huIL-17A/IL-17F antibodies bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (iv) a neutralizing ability of at least 0.2 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.2 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 0.2 nM or less against the IL-17A/IL-17F heterodimeric complex.

The huIL-17A/F antibodies have the following characteristics:

Binding Affinity (pM):

	All* huIL-17A/F Antibodies	**15E6**	**15E6FK**
IL-17A homodimer	100	40	15
IL-17F homodimer	300	10	10
IL-17A/IL-17F heterodimer	400	50	30

* All antibodies refers to the following huIL-17A/F antibodies: 15E6, 15E6FK, 30D12, 30D12BF, 39F12, 39F12A, and 29E8

Neutralizing Ability (nM), as measuring using the MEF cell assay:

	All* huIL-17A/F Antibodies	**All* huIL-17A/F Antibodies, Except 30D12**	**15E6**	**15E6FK**
IL-17A homodimer	13	13	1.6	0.2
IL-17F homodimer	120	1.9	1.7	1.2
IL-17A/IL-17F heterodimer	31	11	1.1	0.2

* All antibodies refers to the following huIL-17A/F antibodies: 15E6, 15E6FK, 30D12, 30D12BF, 39F12, 39F12A, and 29E8

Binding affinity, as referred to herein, was determined using the assays described herein, e.g., in Example 5. Neutralizing ability, as referred to herein, was determined using the mouse embryonic fibroblast cellular assays described herein, e.g., in Example 7.

In a preferred embodiment, the huIL-17A/IL-17F antibodies bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (i) a binding affinity of at least 40 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 10 pM or less against the IL-17F homodimer, (iii) a binding affinity of at least 50 pM or less against the IL-17A/IL-17F heterodimeric complex, (iv) a neutralizing ability of at least 1.6 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.7 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 1.1 nM or less against the IL-17A/IL-17F heterodimeric complex.

In a more preferred embodiment, the huIL-17A/IL-17F antibodies bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (i) a binding affinity of at least 15 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 10 pM or less against the IL-17F homodimer, (iii) a binding affinity of at least 30 pM or less against the IL-17A/IL-17F heterodimeric complex, (iv) a neutralizing ability of at least 0.2 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.2 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 0.2 nM or less against the IL-17A/IL-17F heterodimeric complex.

In a preferred embodiment, the huIL-17A/IL-17F antibody is the 15E6 antibody or an antibody that binds to the same epitope as the 15E6 antibody or otherwise cross-competes with the binding site of the 15E6 antibody. In a more preferred embodiment, the huIL-17A/IL-17F antibody is the 15E6FK antibody or an antibody that binds to the same

epitope as the 15E6 antibody or otherwise cross-competes with the binding site of the 15E6FK antibody. In a most preferred embodiment, the huIL-17A/IL-17F antibody has the binding affinity and neutralizing conditions described above, and binds to the same epitope as the 15E6 antibody or otherwise competes with the binding site of the 15E6 antibody.

Preferably, the huIL-17A/IL-17F antibodies bind to the same epitope as the 15E6 antibody or otherwise competes with the binding site of the 15E6 antibody, and the huIL-17A/IL-17F antibodies also bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (i) a binding affinity of at least 40 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 10 pM or less against the IL-17F homodimer, (iii) a binding affinity of at least 50 pM or less against the IL-17A/IL-17F heterodimeric complex, (iv) a neutralizing ability of at least 1.6 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.7 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 1.1 nM or less against the IL-17A/IL-17F heterodimeric complex.

Preferably, the huIL-17A/IL-17F antibodies bind to the same epitope as the 15E6FK antibody or otherwise competes with the binding site of the 15E6FK antibody, and the huIL-17A/IL-17F antibodies also bind IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, and these antibodies exhibit (i) a binding affinity of at least 15 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 10 pM or less against the IL-17F homodimer, (iii) a binding affinity of at least 30 pM or less against the IL-17A/IL-17F heterodimeric complex, (iv) a neutralizing ability of at least 0.2 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.2 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 0.2 nM or less against the IL-17A/IL-17F heterodimeric complex.

Antibodies of the invention also include fully human antibodies that specifically bind IL-17F, IL-17A and or IL-17A/IL-17F wherein the antibody exhibits greater than 50% inhibition of IL-17F, IL-17A and/or IL-17A/IL-17F mediated pro-inflammatory cytokine production *in vitro*. For example, antibodies of the invention exhibit greater than 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 97%, 98%, or 99% inhibition of IL-6 secretion by IL-17 stimulated cells. As used herein, the term "pro-inflammatory cytokine" refers to those immunoregulatory cytokines that promote inflammation and/or are associated with inflammation. Pro-inflammatory cytokines and chemokines include, for example, IL-6, IL-8, G-CSF, and GM-CSF. Pro-inflammatory chemokines include, for

example, GRO-α, GRO-b, LIX, GCP-2, MIG, IP10, I-TAC, ,and MCP-1, RANTES, Eotaxin, SDF-1, and MIP3a.

The present invention also provides methods of treating or preventing pathologies associated with aberrant IL-17, IL-17A and/or IL-17A/IL-17F activity (*e.g.*, aberrant pro-inflammatory cytokine production such as aberrant IL-6 production), or alleviating a symptom associated with such pathologies, by administering a monoclonal antibody of the invention (*e.g.*, fully human monoclonal antibody) to a subject in which such treatment or prevention is desired. The subject to be treated is, *e.g.*, human. The monoclonal antibody is administered in an amount sufficient to treat, prevent or alleviate a symptom associated with the pathology. The amount of monoclonal antibody sufficient to treat or prevent the pathology in the subject is, for example, an amount that is sufficient to reduce IL-17F, IL-17A and/or IL-17A/IL-17F signaling (*e.g.*, IL-17F induced production of one or more pro-inflammatory cytokines (*e.g.*, IL-6)). As used herein, the term "reduced" refers to a decreased production of a pro-inflammatory cytokine in the presence of a monoclonal antibody of the invention, wherein the production is, for example, local pro-inflammatory cytokine production (*e.g.*, at a site of inflamed tissue) or systemic pro-inflammatory cytokine production. IL-17F, IL-17A and/or IL-17A/IL-17F signaling (*e.g.*, IL-17F induced pro-inflammatory cytokine such as IL-6) is decreased when the level of pro-inflammatory cytokine (*e.g.*, IL-6) production in the presence of a monoclonal antibody of the invention is greater than or equal to 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, 99%, or 100% lower than a control level of pro-inflammatory cytokine production (*i.e.*, the level of pro-inflammatory cytokine production in the absence of the monoclonal antibody). Level of pro-inflammatory cytokine production (*e.g.*, IL-6) is measured, *e.g.*, using the IL-17-stimulated Mouse Embryonic Fibroblasts (MEF) cellular assays described herein. Those skilled in the art will appreciate that the level of pro-inflammatory cytokine production can be measured using a variety of assays, including, for example, commercially available ELISA kits.

Pathologies treated and/or prevented using the monoclonal antibodies of the invention (*e.g.*, fully human monoclonal antibody) include, for example, acute inflammation, chronic inflammation (*e.g.*, chronic inflammation associated with allergic conditions and asthma), autoimmune diseases (*e.g.*, Crohn's disease, multiple sclerosis), inflammatory bowel disease, and transplant rejection.

Pharmaceutical compositions according to the invention can include an antibody of the invention and a carrier. These pharmaceutical compositions can be included in kits, such as, for example, diagnostic kits.

The present invention also provides soluble IL-17F proteins, methods for expressing IL-17F proteins, and methods for purifying such proteins in a soluble form.

In some embodiments, the pathology to be treated is one or more autoimmune diseases inflammatory disorders and cancer. For example, without limitation, the pathology is rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis chronic obstructive pulmonary disease, asthma, angiogenesis and cancer.

Pharmaceutical compositions according to the invention can include an antibody of the invention and a carrier. These pharmaceutical compositions can be included in kits, such as, for example, diagnostic kits.

One skilled in the art will appreciate that the antibodies of the invention have a variety of uses. For example, the proteins of the invention are used as therapeutic agents to prevent the activation of IL-17 receptor and/or IL-17 receptor complexes in disorders such as, for example, rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis chronic obstructive pulmonary disease, asthma, angiogenesis and cancer. The antibodies of the invention are also used as reagents in diagnostic kits or as diagnostic tools, or these antibodies can be used in competition assays to generate therapeutic reagents.

DETAILED DESCRIPTION

The present invention provides monoclonal antibodies that specifically bind IL-17F. The invention further provides monoclonal antibodies that specifically bind IL-17F and IL-17A when not complexed together (*i.e.*, cross-reactive monoclonal antibodies). The invention further provides monoclonal antibodies that specifically bind IL-17F and the heterodimeric IL-17A/IL-17F complex (also referred to herein as the IL-17A/IL-17F heterodimer). The present invention even further provides cross-reactive monoclonal antibodies that bind IL-17F, IL-17A and the heterodimeric IL-17A/IL-17F complex. These antibodies are collectively referred to herein as "huIL-17A/F" antibodies. The antibody is *e.g.*, a fully human antibody.

Antibodies of the invention specifically bind IL-17F, wherein the antibody binds to an epitope that includes one or more amino acid residues of human IL-17F. Antibodies of the invention specifically bind both IL-17F and IL-17A wherein the antibody binds an

epitope that includes one or more amino acid residues of human IL-17F, human IL-17A, or both. Antibodies of the invention specifically bind both IL-17F and the heterodimeric IL-17A/IL-17F complex wherein the antibody binds to an epitope that includes one or more amino acid residues of human IL-17F, IL-17A, or both.

The antibodies of the present invention bind to an IL-17F epitope and/or an IL-17A epitope with an equilibrium binding constant (K_d) of ≤1 μM, *e.g.*, ≤ 100 nM, preferably ≤ 10 nM, and more preferably ≤ 1 nM. For example, the huIL-17A/F antibodies provided herein exhibit a K_d in the range approximately between ≤ 1 nM to about 1 pM.

The crystal structure of IL-17F reveals that the protein adopts a cysteine knot fold, suggesting a relationship to the cysteine knot superfamily of proteins. However, the cysteine knot motif of IL-17F only utilizes four cysteines instead of the classical six cysteines to form the knot. Like other members of the cysteine knot family, IL-17F also exists as a heterodimer with IL-17A. The IL-17A/IL-17F heterodimer is believed to signal through IL-17R and/or the multimeric IL-17R/ IL-17RC complex. Recent evidence has shown that the same cysteine residues that are utilized in forming the IL-17A/IL-17F heterodimer are the same cysteines utilized in the IL-17F homodimer formation. This data suggests that the receptor for the IL-17F homodimer or IL-17A/IL-17F heterodimer may bind to the conserved cysteine residues at the dimer interface, like other proteins in the cysteine knot family.

Numerous immune regulatory functions have been reported for the IL-17 family of cytokines, presumably due to their induction of many immune signaling molecules. IL-17A and IL-17F share very similar biological functions. Both promote secretion of pro-inflammatory cytokines (*e.g.*, IL-6, IL-8, G-CSF, and GM-CSF), chemokines (*e.g.*, GRO-α, GRO-b, LIX, GCP-2, MIG, IP10, I-TAC, and MCP-1, RANTES, Eotaxin, SDF-1, and MIP3a) and prostaglandins (*e.g.*, PGE_2) from a wide variety of cells including fibroblasts, keratinocytes, macrophages, epithelial cells and endothelial cells. Both have also been shown to regulate cartilage matrix turnover. IL-17F also has biological functions distinct from IL-17A such as the ability to stimulate proliferation and activation of T cells and peripheral blood mononuclear cells (PBMCs), and to inhibit angiogenesis.

The huIL-17A/F antibodies of the invention serve to modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with the biological activity of IL-17F, IL-17A and/or the IL-17A/IL-17F heterodimeric complex. Biological activities of IL-17F, IL-17A and/or IL-17A/IL-17F include, for example, binding to IL-17R, IL-17RC and/or the

multimeric IL-17R/IL-17RC receptor complex, and the induction of cytokine and/or chemokine expression (*e.g.*, IL-6, IL-8, G-CSF, GM-CSF, GRO-α, GRO-b, LIX, GCP-2, MIG, IP10, I-TAC, ,and MCP-1, RANTES, Eotaxin, SDF-1, and MIP3a) in target cells. For example, the huIL-17A/F antibodies completely or partially inhibit IL-17F, IL-17A and/or IL-17A/IL-17F biological activity by partially or completely modulating, blocking, inhibiting, reducing antagonizing, neutralizing, or otherwise interfering with the binding of IL-17F, IL-17A and/or IL-17A/IL-17F to their receptors, or otherwise partially or completely modulating, blocking, inhibiting, reducing, antagonizing, neutralizing IL-17F, IL-17A and/or IL-17A/IL-17F complex signaling activity.

The huIL-17A/F antibodies are considered to completely modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with IL-17F, IL-17A and/or IL-17A/IL-17F biological activity when the level of IL-17F, IL-17A and/or IL-17A/IL-17F activity in the presence of the IL-17F antibody is decreased by at least 95%, *e.g.*, by 96%, 97%, 98%, 99% or 100% as compared to the level of IL-17F, IL-17A and/or IL-17A/IL-17F in the absence of binding with an IL-17F antibody described herein. The huIL-17A/F antibodies are considered to partially modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with IL-17F, IL-17A and/or IL-17A/IL-17F activity when the level of IL-17F, IL-17A and/or IL-17A/IL-17F activity in the presence of the IL-17F antibody is decreased by less than 95%, *e.g.*, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 85% or 90% as compared to the level of IL-17F, IL-17A and/or IL-17A/IL-17F activity in the absence of binding with an IL-17F antibody described herein.

The huIL-17A/F cross-reactive antibodies are considered to completely modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with IL-17F, IL-17A and/or IL-17A/IL-17F activity when the level of IL-17F, IL-17A and/or IL-17A/IL-17F activity in the presence of the IL-17F antibody is decreased by at least 95%, *e.g.*, by 96%, 97%, 98%, 99% or 100% as compared to the level of IL-17F, IL-17A and/or IL-17A/IL-17F activity in the absence of binding with an IL-17F antibody described herein. The IL-17F cross-reactive antibodies are considered to partially modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with IL-17F, IL-17A and/or IL-17A/IL-17F activity when the level of IL-17F, IL-17A and/or IL-17A/IL-17F activity in the presence of the IL-17F antibody is decreased by less than 95%, *e.g.*, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 75%, 80%, 85% or 90% as compared to the level of IL-17F, IL-17A and/or IL-17A/IL-17F activity in the absence of binding with an IL-17F antibody described herein.

Definitions

Unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (*e.g.,* electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. *See e.g.,* Sambrook *et al.* Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

As used herein, the terms Interleukin-17A, IL-17A, IL17A, IL-17, IL17, CTLA8, CTLA-8, Cytotoxic T-lymphocyte-associated antigen 8 and Interleukin-17A precursor are synonymous and may be used interchangeably. Each of these terms refers to the homodimeric protein, except where otherwise indicated.

As used herein, the terms Interleukin-17F, IL-17F, IL17F, ML-1, ML1, Interleukin-24, IL-24, IL24 and Interleukin-17F precursor are synonymous and may be used interchangeably. Each of these terms refers to the homodimeric protein, except where otherwise indicated.

As used herein, the term "antibody" refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. By

"specifically bind" or "immunoreacts with" or "directed against" is meant that the antibody reacts with one or more antigenic determinants of the desired antigen and does not react with other polypeptides or binds at much lower affinity ($K_d > 10^{-6}$). Antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, dAb (domain antibody), single chain, F_{ab}, $F_{ab'}$ and $F_{(ab')2}$ fragments, scFvs, and an F_{ab} expression library.

The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. In general, antibody molecules obtained from humans relate to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG_1, IgG_2, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain.

The term "monoclonal antibody" (MAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

In general, antibody molecules obtained from humans relate to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG_1, IgG_2, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain.

The term "antigen-binding site" or "binding portion" refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains, referred to as "hypervariable regions," are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus, the term "FR" refers to amino acid sequences which are naturally found between, and adjacent to, hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable

regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." The assignment of amino acids to each domain is in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk J. Mol. Biol. 196:901-917 (1987), Chothia *et al.* Nature 342:878-883 (1989).

As used herein, the term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or fragment thereof, or a T-cell receptor. The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is $\leq$ 1 μM; *e.g.*, $\leq$ 100 nM, preferably $\leq$ 10 nM and more preferably $\leq$ 1 nM.

As used herein, the terms "immunological binding," and "immunological binding properties" refer to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. (*See* Nature 361:186-87 (1993)). The ratio of K_{off} /K_{on} enables the cancellation of all parameters not related to affinity, and is equal to the dissociation constant K_d. (*See, generally*, Davies et al. (1990) Annual Rev Biochem 59:439-473). An antibody of the present invention is said to specifically bind to IL-17F homodimer, IL-A homodimer and/or the IL-17A/IL-17F

heterodimer, when the equilibrium binding constant (K_d) is ≤1 μM, preferably ≤ 100 nM, more preferably ≤ 10 nM, and most preferably ≤ 100 pM to about 1 pM, as measured by assays such as radioligand binding assays or similar assays known to those skilled in the art.

The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the "isolated polynucleotide" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence. Polynucleotides in accordance with the invention include the nucleic acid molecules encoding the heavy chain immunoglobulin molecules presented in SEQ ID NOS: 2, 6, 8, 10, 14, 18, 20, 24, 28, 32, 34, 38, 44, 48 or 54 and nucleic acid molecules encoding the light chain immunoglobulin molecules represented in SEQ ID NOS: SEQ ID NOS: 4, 12, 16, 22, 26, 30, 36, 40, 46 or 56.

The term "isolated protein" referred to herein means a protein of cDNA, recombinant RNA, or synthetic origin or some combination thereof, which by virtue of its origin, or source of derivation, the "isolated protein" (1) is not associated with proteins found in nature, (2) is free of other proteins from the same source, *e.g.,* free of marine proteins, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

The term "polypeptide" is used herein as a generic term to refer to native protein, fragments, or analogs of a polypeptide sequence. Hence, native protein fragments, and analogs are species of the polypeptide genus. Polypeptides in accordance with the invention comprise the heavy chain immunoglobulin molecules represented in SEQ ID NOS: 2, 6, 8, 10, 14, 18, 20, 24, 28, 32, 34, 38, 44, 48, or 54 and the light chain immunoglobulin molecules represented in SEQ ID NOS: SEQ ID NOS: 4, 12, 16, 22, 26, 30, 36, 40, 46, 50 or 56, as well as antibody molecules formed by combinations comprising the heavy chain immunoglobulin molecules with light chain immunoglobulin molecules, such as kappa light chain immunoglobulin molecules, and vice versa, as well as fragments and analogs thereof.

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

The term "operably linked" as used herein refers to positions of components so described are in a relationship permitting them to function in their intended manner. A control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences.

The term "control sequence" as used herein refers to polynucleotide sequences which are necessary to effect the expression and processing of coding sequences to which they are ligated. The nature of such control sequences differs depending upon the host organism in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. The term "polynucleotide" as referred to herein means a polymeric boron of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA.

The term "oligonucleotide" referred to herein includes naturally occurring, and modified nucleotides linked together by naturally occurring, and non-naturally occurring oligonucleotide linkages. Oligonucleotides are a polynucleotide subset generally comprising a length of 200 bases or fewer. Preferably oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 bases in length. Oligonucleotides are usually single stranded, *e.g.,* for probes, although oligonucleotides may be double stranded, *e.g.,* for use in the construction of a gene mutant. Oligonucleotides of the invention are either sense or antisense oligonucleotides.

The term "naturally occurring nucleotides" referred to herein includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" referred to herein includes Oligonucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselerloate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate, phosphoronmidate, and the like. *See e.g.,* LaPlanche *et al.* Nucl. Acids Res. 14:9081 (1986); Stec *et al.* J. Am. Chem. Soc. 106:6077 (1984), Stein *et al.* Nucl. Acids Res. 16:3209 (1988), Zon *et al.* Anti Cancer Drug Design 6:539 (1991); Zon *et al.* Oligonucleotides and Analogues: A Practical Approach, pp. 87-108

(F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec *et al.* U.S. Patent No. 5,151,510; Uhlmann and Peyman Chemical Reviews 90:543 (1990). An oligonucleotide can include a label for detection, if desired.

The term "selectively hybridize" referred to herein means to detectably and specifically bind. Polynucleotides, oligonucleotides and fragments thereof in accordance with the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. High stringency conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic acid sequence homology between the polynucleotides, oligonucleotides, and fragments of the invention and a nucleic acid sequence of interest will be at least 80%, and more typically with preferably increasing homologies of at least 85%, 90%, 95%, 99%, and 100%. Two amino acid sequences are homologous if there is a partial or complete identity between their sequences. For example, 85% homology means that 85% of the amino acids are identical when the two sequences are aligned for maximum matching. Gaps (in either of the two sequences being matched) are allowed in maximizing matching gap lengths of 5 or less are preferred with 2 or less being more preferred. Alternatively and preferably, two protein sequences (or polypeptide sequences derived from them of at least 30 amino acids in length) are homologous, as this term is used herein, if they have an alignment score of at more than 5 (in standard deviation units) using the program ALIGN with the mutation data matrix and a gap penalty of 6 or greater. *See* Dayhoff, M.O., in Atlas of Protein Sequence and Structure, pp. 101-110 (Volume 5, National Biomedical Research Foundation (1972)) and Supplement 2 to this volume, pp. 1-10. The two sequences or parts thereof are more preferably homologous if their amino acids are greater than or equal to 50% identical when optimally aligned using the ALIGN program. The term "corresponds to" is used herein to mean that a polynucleotide sequence is homologous (*i.e.,* is identical, not strictly evolutionarily related) to all or a portion of a reference polynucleotide sequence, or that a polypeptide sequence is identical to a reference polypeptide sequence. In contradistinction, the term "complementary to" is used herein to mean that the complementary sequence is homologous to all or a portion of a reference polynucleotide sequence. For illustration, the nucleotide sequence "TATAC" corresponds to a reference sequence "TATAC" and is complementary to a reference sequence "GTATA".

The following terms are used to describe the sequence relationships between two or more polynucleotide or amino acid sequences: "reference sequence", "comparison window",

"sequence identity", "percentage of sequence identity", and "substantial identity". A "reference sequence" is a defined sequence used as a basis for a sequence comparison a reference sequence may be a subset of a larger sequence, for example, as a segment of a full-length cDNA or gene sequence given in a sequence listing or may comprise a complete cDNA or gene sequence. Generally, a reference sequence is at least 18 nucleotides or 6 amino acids in length, frequently at least 24 nucleotides or 8 amino acids in length, and often at least 48 nucleotides or 16 amino acids in length. Since two polynucleotides or amino acid sequences may each (1) comprise a sequence (*i.e.,* a portion of the complete polynucleotide or amino acid sequence) that is similar between the two molecules, and (2) may further comprise a sequence that is divergent between the two polynucleotides or amino acid sequences, sequence comparisons between two (or more) molecules are typically performed by comparing sequences of the two molecules over a "comparison window" to identify and compare local regions of sequence similarity. A "comparison window", as used herein, refers to a conceptual segment of at least 18 contiguous nucleotide positions or 6 amino acids wherein a polynucleotide sequence or amino acid sequence may be compared to a reference sequence of at least 18 contiguous nucleotides or 6 amino acid sequences and wherein the portion of the polynucleotide sequence in the comparison window may comprise additions, deletions, substitutions, and the like (*i.e.,* gaps) of 20 percent or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by the local homology algorithm of Smith and Waterman Adv. Appl. Math. 2:482 (1981), by the homology alignment algorithm of Needleman and Wunsch J. Mol. Biol. 48:443 (1970), by the search for similarity method of Pearson and Lipman Proc. Natl. Acad. Sci. (U.S.A.) 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, (Genetics Computer Group, 575 Science Dr., Madison, Wis.), Geneworks, or MacVector software packages), or by inspection, and the best alignment (*i.e.,* resulting in the highest percentage of homology over the comparison window) generated by the various methods is selected.

The term "sequence identity" means that two polynucleotide or amino acid sequences are identical (*i.e.,* on a nucleotide-by-nucleotide or residue-by-residue basis) over the comparison window. The term "percentage of sequence identity" is calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (*e.g.,* A, T, C, G, U or I) or

residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the comparison window (*i.e.,* the window size), and multiplying the result by 100 to yield the percentage of sequence identity. The terms "substantial identity" as used herein denotes a characteristic of a polynucleotide or amino acid sequence, wherein the polynucleotide or amino acid comprises a sequence that has at least 85 percent sequence identity, preferably at least 90 to 95 percent sequence identity, more usually at least 99 percent sequence identity as compared to a reference sequence over a comparison window of at least 18 nucleotide (6 amino acid) positions, frequently over a window of at least 24-48 nucleotide (8-16 amino acid) positions, wherein the percentage of sequence identity is calculated by comparing the reference sequence to the sequence which may include deletions or additions which total 20 percent or less of the reference sequence over the comparison window. The reference sequence may be a subset of a larger sequence.

As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. *See* Immunology - A Synthesis (2nd Edition, E.S. Golub and D.R. Gren, Eds., Sinauer Associates, Sunderland7 Mass. (1991)). Stereoisomers (*e.g.,* D- amino acids) of the twenty conventional amino acids, unnatural amino acids such as α-, α-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4 hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε -N-acetyllysine, O-phosphoserine, N- acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (*e.g.,* 4- hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

Similarly, unless specified otherwise, the left-hand end of single- stranded polynucleotide sequences is the 5' end the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction sequence regions on the DNA strand having the same sequence as the RNA and which are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences", sequence regions on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences".

As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80 percent sequence identity, preferably at least 90 percent sequence identity, more preferably at least 95 percent sequence identity, and most preferably at least 99 percent sequence identity.

Preferably, residue positions which are not identical differ by conservative amino acid substitutions.

Conservative amino acid substitutions refer to the interchangeability of residues having similar side chains. For example, a group of amino acids having aliphatic side chains is glycine, alanine, valine, leucine, and isoleucine; a group of amino acids having aliphatic-hydroxyl side chains is serine and threonine; a group of amino acids having amide-containing side chains is asparagine and glutamine; a group of amino acids having aromatic side chains is phenylalanine, tyrosine, and tryptophan; a group of amino acids having basic side chains is lysine, arginine, and histidine; and a group of amino acids having sulfur-containing side chains is cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine valine, glutamic- aspartic, and asparagine-glutamine.

As discussed herein, minor variations in the amino acid sequences of antibodies or immunoglobulin molecules are contemplated as being encompassed by the present invention, providing that the variations in the amino acid sequence maintain at least 75%, more preferably at least 80%, 90%, 95%, and most preferably 99%. In particular, conservative amino acid replacements are contemplated. Conservative replacements are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids are generally divided into families: (1) acidic amino acids are aspartate, glutamate; (2) basic amino acids are lysine, arginine, histidine; (3) non-polar amino acids are alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, and (4) uncharged polar amino acids are glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. The hydrophilic amino acids include arginine, asparagine, aspartate, glutamine, glutamate, histidine, lysine, serine, and threonine. The hydrophobic amino acids include alanine, cysteine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, tyrosine and valine. Other families of amino acids include (i) serine and threonine, which are the aliphatic-hydroxy family; (ii) asparagine and glutamine, which are the amide containing family; (iii) alanine, valine, leucine and isoleucine, which are the aliphatic family; and (iv) phenylalanine, tryptophan, and tyrosine,

which are the aromatic family. For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the binding or properties of the resulting molecule, especially if the replacement does not involve an amino acid within a framework site. Whether an amino acid change results in a functional peptide can readily be determined by assaying the specific activity of the polypeptide derivative. Assays are described in detail herein. Fragments or analogs of antibodies or immunoglobulin molecules can be readily prepared by those of ordinary skill in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Preferably, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. Bowie *et al.* Science 253:164 (1991). Thus, the foregoing examples demonstrate that those of skill in the art can recognize sequence motifs and structural conformations that may be used to define structural and functional domains in accordance with the invention.

Preferred amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (4) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various muteins of a sequence other than the naturally-occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally- occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (*e.g.,* a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in Proteins, Structures and Molecular Principles (Creighton, Ed., W. H. Freeman and Company, New York (1984)); Introduction to Protein Structure (C. Branden

and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et at. Nature 354:105 (1991).

The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino terminal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally-occurring sequence deduced, for example, from a full length cDNA sequence. Fragments typically are at least 5, 6, 8 or 10 amino acids long, preferably at least 14 amino acids long' more preferably at least 20 amino acids long, usually at least 50 amino acids long, and even more preferably at least 70 amino acids long. The term "analog" as used herein refers to polypeptides which are comprised of a segment of at least 25 amino acids that has substantial identity to a portion of a deduced amino acid sequence and which has specific binding to IL-17F alone or IL-17A/IL-17F heterodimer (*i.e.*, complex), under suitable binding conditions. Typically, polypeptide analogs comprise a conservative amino acid substitution (or addition or deletion) with respect to the naturally- occurring sequence. Analogs typically are at least 20 amino acids long, preferably at least 50 amino acids long or longer, and can often be as long as a full-length naturally-occurring polypeptide.

Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics". Fauchere, J. Adv. Drug Res. 15:29 (1986), Veber and Freidinger TINS p.392 (1985); and Evans *et al.* J. Med. Chem. 30:1229 (1987). Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.,* a polypeptide that has a biochemical property or pharmacological activity), such as human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: -- CH_2NH--, --CH_2S-, --CH_2-CH_2--, --CH=CH--(cis and trans), --$COCH_2$--, $CH(OH)CH_2$--, and -CH_2SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.,* D-lysine in place of L-lysine) may be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch Ann. Rev. Biochem. 61:387 (1992)); for example, by adding

internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

As used herein, the terms "label" or "labeled" refers to incorporation of a detectable marker, *e.g.,* by incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (*e.g.,* streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or calorimetric methods). In certain situations, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (*e.g.,* ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent labels (*e.g.,* FITC, rhodamine, lanthanide phosphors), enzymatic labels (*e.g.,* horseradish peroxidase, p-galactosidase, luciferase, alkaline phosphatase), chemiluminescent, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (*e.g.,* leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance. The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient.

Other chemistry terms herein are used according to conventional usage in the art, as exemplified by The McGraw-Hill Dictionary of Chemical Terms (Parker, S., Ed., McGraw-Hill, San Francisco (1985)).

The term "antineoplastic agent" is used herein to refer to agents that have the functional property of inhibiting a development or progression of a neoplasm in a human, particularly a malignant (cancerous) lesion, such as a carcinoma, sarcoma, lymphoma, or leukemia. Inhibition of metastasis is frequently a property of antineoplastic agents.

As used herein, "substantially pure" means an object species is the predominant species present (*i.e.,* on a molar basis it is more abundant than any other individual species in the composition), and preferably a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species present.

Generally, a substantially pure composition will comprise more than about 80 percent of all macromolecular species present in the composition, more preferably more than about 85%, 90%, 95%, and 99%. Most preferably, the object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

Autoimmune diseases include, for example, Acquired Immunodeficiency Syndrome (AIDS, which is a viral disease with an autoimmune component), alopecia areata, ankylosing spondylitis, antiphospholipid syndrome, autoimmune Addison's disease, autoimmune hemolytic anemia, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune lymphoproliferative syndrome (ALPS), autoimmune thrombocytopenic purpura (ATP), Behcet's disease, cardiomyopathy, celiac sprue-dermatitis hepetiformis; chronic fatigue immune dysfunction syndrome (CFIDS), chronic inflammatory demyelinating polyneuropathy (CIPD), cicatricial pemphigold, cold agglutinin disease, crest syndrome, Crohn's disease, Degos' disease, dermatomyositis-juvenile, discoid lupus, essential mixed cryoglobulinemia, fibromyalgia-fibromyositis, Graves' disease, Guillain-Barré syndrome, Hashimoto's thyroiditis, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia purpura (ITP), IgA nephropathy, insulin-dependent diabetes mellitus, juvenile chronic arthritis (Still's disease), juvenile rheumatoid arthritis, Ménière's disease, mixed connective tissue disease, multiple sclerosis, myasthenia gravis, pernacious anemia, polyarteritis nodosa, polychondritis, polyglandular syndromes, polymyalgia rheumatica, polymyositis and dermatomyositis, primary agammaglobulinemia, primary biliary cirrhosis, psoriasis, psoriatic arthritis, Raynaud's phenomena, Reiter's syndrome, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma (progressive systemic sclerosis (PSS), also known as systemic sclerosis (SS)), Sjögren's syndrome, stiff-man syndrome, systemic lupus erythematosus, Takayasu arteritis, temporal arteritis/giant cell arteritis, ulcerative colitis, uveitis, vitiligo and Wegener's granulomatosis.

Inflammatory disorders include, for example, chronic and acute inflammatory disorders. Examples of inflammatory disorders include Alzheimer's disease, asthma, atopic allergy, allergy, atherosclerosis, bronchial asthma, eczema, glomerulonephritis, graft vs. host disease, hemolytic anemias, osteoarthritis, sepsis, stroke, transplantation of tissue and organs, vasculitis, diabetic retinopathy and ventilator induced lung injury.

huIL-17F -A Antibodies

Monoclonal antibodies of the invention (*e.g.*, fully human monoclonal antibodies) have the ability to inhibit IL-17F, IL-17A and/or IL-1F/IL-17A-induced proinflammatory cytokine production (*e.g.*, IL-6). Inhibition is determined, for example, the IL-17 stimulated mouse embryonic fibroblast (MEF) cellular assays described herein.

Exemplary antibodies of the invention include, for example, the 30D12 antibody, the 29D8 antibody, the 1E4 antibody, the 31A3 antibody, the 39F12 antibody, the 12B12 antibody, the 15B7 antibody, the 4H11 antibody, the 4B11 antibody, the 8B11 antibody, the 38B1 antibody, and the 15E6 antibody, the 5E12 antibody, the 41B10 antibody, and variants thereof. Variants of such antibodies include the 30D12BF antibody (a variant of the 30D12 antibody), the 39F12A antibody (a variant of the 39F12 antibody), and the 15E6FK antibody (a variant of the 15E6 antibody). These antibodies show specificity for human IL-17F and they have been shown to inhibit human IL-17F induction of the pro-inflammatory cytokine IL-6 *in vitro*. The 29D8 antibody ("Mab02a"), the 1E4 ("Mab02b") antibody, the 31A3 antibody ("Mab02c"), the 39F12 antibody ("Mab06a"), the 12B12 antibody ("Mab06b"), the 15B7 antibody ("Mab06c"), the 4H11 antibody ("Mab09"), the 30D12 antibody, the 8B11 antibody, the 38B1 antibody, the 15E6 antibody and the 4B11 antibody also show specificity for human IL-17A and have been shown to inhibit human IL-17A induced IL-6 production *in vitro*. The 29D8 antibody, the 1E4 antibody, the 31A3 antibody, the 39F12 antibody, the 12B12 antibody, the 15B7 antibody, the 4H11 antibody, the 30D12 antibody, the 8B11 antibody, the 38B1 antibody, the 15E6 antibody and the 4B11 antibody also show specificity for the human IL-17A/IL-17F heterodimeric complex. The 5E12 antibody binds human IL-17F, but does not bind human IL-17A, the IL-17A homodimer or the human IL-17A/IL-17F heterodimeric complex. The 41B10 antibody binds human IL-17F and the human IL-17A/IL-17F heterodimeric complex, but does not bind human IL-17A or the IL-17A homodimer.

Each of the huIL-17F monoclonal antibodies described herein includes a heavy chain variable region (VH) and a light chain variable region (VL), as shown in the amino acid and corresponding nucleic acid sequences listed below. The 30D12 antibody includes a heavy chain variable region (SEQ ID NO:2) encoded by the nucleic acid sequence shown in SEQ ID NO:1, and a light chain variable region (SEQ ID NO:4) encoded by the nucleic acid sequence shown in SEQ ID NO:3.

>30D12 VH nucleic acid sequence (SEQ ID NO:1)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC
TGGATACACCTTCACCAGTTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGAT
GGATGAACCCTGACAGTGGTGTCATACGTTATGCACAGAAGTTCCAGGGTAGAGTCACCATGACCAGGAACACC
TCCATAAGCACAGCCTACATGGAGCTAAACAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGA
ATGGTTCGGGGAGTTACCCTCTTACTACTTCTACTCCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCG
TCTCCTCA

>30D12 VH amino acid sequence (SEQ ID NO:2)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWMGWMNPDSGVIRYAQKFQGRVTMTRNT
SISTAYMELNSLRSEDTAVYYCAREWFGELPSYYFYSGMDVWGQGTTVTVSS

>30D12 VL nucleic acid sequence (SEQ ID NO:3)

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGC
CAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG
ATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC
ATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCTCCCACTTTCGG
CCCTGGGACCAAAGTGGATATCAAA

>30D12 VL amino acid sequence (SEQ ID NO:4)

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT
ISSLEPEDFAVYYCQQRSNWPPTFGPGTKVDIK

The 29D8, 1E4 and 31A3 antibodies each include a distinct heavy chain variable region, but share common light chain variable region. The 29D8 antibody includes a heavy chain variable region (SEQ ID NO:6) encoded by the nucleic acid sequence shown in SEQ ID NO:5. The 1E4 antibody includes a heavy chain variable region (SEQ ID NO: 8) encoded by the nucleic acid sequence shown in SEQ ID NO:7. The 31A3 antibody includes a heavy chain variable region (SEQ ID NO:10) encoded by the nucleic acid sequence shown in SEQ ID NO:9). The light chain variable region for the 29D8, 1E4 and 31A3 antibodies (SEQ ID NO:12) is encoded by the nucleic acid sequence shown in SEQ ID NO:11.

>29D8 VH nucleic acid sequence(SEQ ID NO:5)

CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTT
TGCTTACACCTTTTCCACCTATGGTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAT
GGATCAGCGCTTACAATAGTAACACAAACTATGCACAGAAAGTCCAGGGCAGAATCACCATGACCACAGACACA
TCCACGCGCACAGCCTACATGGAGCTGAGGGGCCTGAGATCTGACGACACGGCCGTGTATTTCTGTGCGACTTT
CTTCGGTGGTCACTCTGGCTACCACTACGGGTTGGACGTCTGGGGCCAGGGGACCACGGTCACCGTCTCCTCA

>29D8 VH amino acid sequence(SEQ ID NO:6)

QVQLVQSGAEVKKPGASVKVSCKAFAYTFSTYGISWVRQAPGQGLEWMGWISAYNSNTNYAQKVQGRITMTTDT
STRTAYMELRGLRSDDTAVYFCATFFGGHSGYHYGLDVWGQGTTVTVSS

>1E4 VH nucleic acid sequence(SEQ ID NO:7)

CAGGTTCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTTTCCTGCAAGGCTTC
TGTTTACACCTTTACCACTTATGGTATCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAT
GGATCAGCGTTTACAATGGTAATACAAACTATGGACAGAATTTCCAGGGCAGAGTCAGCATGACCACAGACACA
TCCACGAGCACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGAGTTT
CCACGGTGGTCACTCTGGCTACCACTACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

>1E4 VH amino acid sequence (SEQ ID NO:8)

QVQLVQSGAEVKKPGASVKVSCKASVYTFTTYGISWVRQAPGQGLEWMGWISVYNGNTNYGQNFQGRVSMTTDT
STSTAYMELRSLRSDDTAVYYCASFHGGHSGYHYGLDVWGQGTTVTVSS

>31A3 VH nucleic acid sequence (SEQ ID NO:9)

CAGGTGCAGCTGGTGCAGTCTGGAGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC
TGTTTACACCTTTACCACCTATGGTATCAGTTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAT
GGATCACCGTTTACAATGGTAACACAAACTATGCACAGAAGTTCCACGGCAGAGTCACCATGACCACAGACACA
TCCACAAGTACAGCCTACATGGAGCTGAGGAGCCTGAGATCTGACGACACGGCCGTCTATTACTGTGCGAGTTT
CCACGGTGGTCATTCTGGCTACCACTACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

>31A3 VH amino acid sequence (SEQ ID NO:10)

QVQLVQSGAEVKKPGASVKVSCKASVYTFTTYGISWVRQAPGQGLEWMGWITVYNGNTNYAQKFHGRVTMTTDT
STSTAYMELRSLRSDDTAVYYCASFHGGHSGYHYGLDVWGQGTTVTVSS

>29D8, 1E4 and 31A3 VL nucleic acid sequence (SEQ ID NO:11)

GAAATTGTGTTGACNCAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGC
CAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATNTATG
ATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC
ATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCTCCGTACACTTT
TGGCCAGGGGACCAAGCTGGAGATCAAA

>29D8, 1E4 and 31A3 VL amino acid sequence (SEQ ID NO:12)

EIVLXQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLXYDASNRATGIPARFSGSGSGTDFTLT
ISSLEPEDFAVYYCQQRSNWPPYTFGQGTKLEIK

The 4B11 antibody includes a heavy chain variable region (SEQ ID NO:14) encoded by the nucleic acid sequence shown in SEQ ID NO:13, and a light chain variable region (SEQ ID NO:16) encoded by the nucleic acid sequence shown in SEQ ID NO:15.

>4B11 VH nucleic acid sequence (SEQ ID NO:13)

CAGCTGCAGTTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCGCTGTCTC
TGATGACTACATCAGCAGTAGGAGTTACTACTGGGGCTGGATCCGCCAGCCCCCAGGGAAGGGGCTGGAGTGGA
TTGGGAGTATCTATTATAGTGGGAGCACCTACTACAACCCGTCCCTCAAGAGTCGAGTCACCATATCCGTAGAC
ACGTCCAAGAACCAGTTCTCCCTGAAAGTGAGTTCTGTGACCGCCACAGACACGGCTGTGTATTACTGTGCGAG
AGTCAGTGGCTGGAACGGGAACTGGTTCGACCCCTGGGGCCAGGGAACCCTGGTCACGGTCTCCTCA

>4B11 VH amino acid sequence (SEQ ID NO:14)

QLQLQESGPGLVKPSETLSLTCAVSDDYISSRSYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSL
KVSSVTATDTAVYYCARVSGWNGNWFDPWGQGTLVTVSS

>4B11 VL nucleic acid sequence (SEQ ID NO:15)

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGC
CAGTCAGAGTGTTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCT
ATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC
ACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCGATCACCTT
CGGCCAAGGGACACGACTGGAGATTAAA

>4B11 VL amino acid sequence (SEQ ID NO:16)

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPE
DFAVYYCQQYGSSPITFGQGTRLEIK

The 39F12 and 12B12 antibodies each include a distinct heavy chain variable region, but share common light chain variable region. The 39F12 antibody includes a heavy chain variable region (SEQ ID NO:18) encoded by the nucleic acid sequence shown in SEQ ID NO:17. The 12B12 antibody includes a heavy chain variable region (SEQ ID NO: 20) encoded by the nucleic acid sequence shown in SEQ ID NO:19. The light chain variable region for the 39F12 and 12B12 antibodies (SEQ ID NO:22) is encoded by the nucleic acid sequence shown in SEQ ID NO:21.

>39F12 VH nucleic acid sequence (SEQ ID NO:17)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTC
TGGAGGCACCCTCAGCAGCTATGCTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAG
GGATCATCCCTTTCTTTGGAACAACAAATTACGCACAGAAGTTCCAGGGCAGAGTCATAATTACCGCGGACGAA
TCCACGAACACAGCCTACATGGAGCTGAGCGGCCTGAGATCTGAGGACACGGCCGTGTATTATTGTGCGAGAGA
CAGGGATTACTATGGTTTGGGGAGTCCCTTCTACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCA
CCGTCTCCTCA

>39F12 VH amino acid sequence (SEQ ID NO:18)

QVQLVQSGAEVKKPGSSVKVSCKASGGTLSSYAFSWVRQAPGQGLEWMGGIIPFFGTTNYAQKFQGRVIITADE
STNTAYMELSGLRSEDTAVYYCARDRDYYGLGSPFYYYGMDVWGQGTTVTVSS

>12B12 VH nucleic acid sequence (SEQ ID NO:19)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTC
TGGAGGCACCCTCAGCAGCTATGCTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGCCTTGAGTGGATGGGAG
GGATCATCCCTTTCTTTGGAACAGTAAACTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAA
TCCACGAACACTGCCTATATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGA
CAGGGATTATTATGGTTTGGGGAGTCCCCTCCACTACTACGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCA
CCGTCTCCTCA

>12B12 VH amino acid sequence (SEQ ID NO:20)

QVQLVQSGAEVKKPGSSVKVSCKASGGTLSSYAFSWVRQAPGQGLEWMGGIIPFFGTVNYAQKFQGRVTITADE
STNTAYMELSSLRSEDTAVYYCARDRDYYGLGSPLHYYGLDVWGQGTTVTVSS

>39F12 and 12B12 VL nucleic acid sequence (SEQ ID NO:21)

GAAATTGTGTTGACACAGTCTCCAGACTTTCAGTCTGTGACTCCAAAGGAGAAAGTCACCATCACCTGCCGGGC
CAGTCAGAGCATTGGTAGTAGCTTACACTGGTACCAGCAGAAACCAGATCAGTCTCCAAAGCTCCTCATCAAGT
ATGCTTCCCAGTCCTTCTCAGGGGTCCCCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACCCTCACC
ATCAATAGCCTGGAAGCTGAAGATGCTGCAGCGTATTACTGTCATCAGAGTAGTAGTTTACCGTGGACGTTCGG
CCAAGGGACCAAGGTGGAAATCAAA

>39F12 and 12B12 VL amino acid sequence (SEQ ID NO:22)

EIVLTQSPDFQSVTPKEKVTITCRASQSIGSSLHWYQQKPDQSPKLLIKYASQSFSGVPSRFSGSGSGTDFTLT
INSLEAEDAAAYYCHQSSSLPWTFGQGTKVEIK

The 4H11 antibody includes a heavy chain variable region (SEQ ID NO:28) encoded by the nucleic acid sequence shown in SEQ ID NO:27, and a light chain variable region (SEQ ID NO: 30) encoded by the nucleic acid sequence shown in SEQ ID NO:29.

>4H11 VH nucleic acid sequence (SEQ ID NO:23)

GAGGTGCAGCTGGTGGAGTCCGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAAACTCTCCTGTGCAGCCTC
TGGGTTCACCTTCAGTGGCTCTTCTATGCACTGGGTCCGCCAGGCTTCCGGGAAAGGGCTGGACTGGGTTGGCC
GTATTAGAAGCAAAGCTAACAGTTACGCGACAGCATATGCTGCGTCGGTGATAGGCAGGTTCACCATCTCCAGA
GATGATTCAAAGAACACGGCGTATCTGCAAATGAACAGCCTGAAAACCGAGGACACGGCCGTGTATTACTGTAC
TACATCAGTGGCTACTACCCTTACTGACTACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT
CCTCA

>4H11 VH amino acid sequence (SEQ ID NO:24)

EVQLVESGGGLVQPGGSLKLSCAASGFTFSGSSMHWVRQASGKGLDWVGRIRSKANSYATAYAASVIGRFTISR
DDSKNTAYLQMNSLKTEDTAVYYCTTSVATTLTDYYGMDVWGQGTTVTVSS

>4H11 VL nucleic acid sequence (SEQ ID NO:25)

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGC
CAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG
ATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC
ATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAACAGCGTAGCAACTGGCCTCCATTCACTTT
CGGCCCTGGGACCAAAGTGGATATCAAA

>4H11 VL amino acid sequence (SEQ ID NO:26)

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT
ISSLEPEDFAVYYCQQRSNWPPFTFGPGTKVDIK

The 8B11 antibody includes a heavy chain variable region (SEQ ID NO:32) encoded by the nucleic acid sequence shown in SEQ ID NO:31, and a light chain variable region (SEQ ID NO:34) encoded by the nucleic acid sequence shown in SEQ ID NO:33.

>8B11 VH nucleic acid sequence (SEQ ID NO:27)

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACACCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCACCTTCAGTAGCTTTAACATGGACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCAT
CCATTAGTACTACTAGCAGAATCATATACTCTGCAGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAAT
GCCAGGAACTCACTGTATCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTATATTACTGTGCGAGAGT
CAGTTACTATGGCCACGGATTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

>8B11 VH amino acid sequence (SEQ ID NO:28)

EVQLVESGGGLVHPGGSLRLSCAASGFTFSSFNMDWVRQAPGKGLEWVSSISTTSRIIYSADSVKGRFTISRDN
ARNSLYLQMNSLRDEDTAVYYCARVSYYGHGFDYWGQGTLVTVSS

>8B11 VL nucleic acid sequence (SEQ ID NO:29)

GACATCCAGATGACCCAGTCTCCATCCTCACTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCGGGC
GAGTCAGGGTATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGAGAAAGCCCCTAAGTCCCTGATCTATG
CTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC
ATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGCCAACAGTATAATAGTTACCCTCTCACTTTCGG
CGGAGGGACCAAGGTGGAGATCAAA

>8B11 VL amino acid sequence (SEQ ID NO:30)

DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLT
ISSLQPEDFATYYCQQYNSYPLTFGGGTKVEIK

The 15B7 antibody includes a distinct heavy chain variable region (SEQ ID NO:36) encoded by the nucleic acid sequence shown in SEQ ID NO:35, and shares a light chain

variable region in common with the 39F12 and 12B12 antibodies (SEQ ID NO:22), encoded by the nucleic acid sequence shown in SEQ ID NO:21, previously shown.

>15B7 VH nucleic acid sequence (SEQ ID NO:31)

CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTC
TGGAGGCACCCTCAGCAGCTATGCTTTCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAG
GAATCATCCCTTTCTTTGGAACAGCACACTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAA
TCCACGAACACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTATATTACTGTGCGAGAGA
TAGGGACTACTATGGTTCGGGGAGTCCCTTCCACTTCTCCGGTTTGGACGTCTGGGGCCAAGGGACCACGGTCA
CCGTCTCCTCA

>15B7 VH amino acid sequence (SEQ ID NO:32)

QVQLVQSGAEVKKPGSSVKVSCKASGGTLSSYAFSWVRQAPGQGLEWMGGIIPFFGTAHYAQKFQGRVTITADE
STNTAYMELSSLRSEDTAVYYCARDRDYYGSGSPFHFSGLDVWGQGTTVTVSS

The 38B1 antibody includes a distinct heavy chain variable region (SEQ ID NO:34) encoded by the nucleic acid sequence shown in SEQ ID NO:33, and a light chain variable region (SEQ ID NO:36) encoded by the nucleic acid sequence shown in SEQ ID NO:35

>38B1 VH nucleic acid sequence (SEQ ID NO:33)

GAAGTACAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCACCTTTGATGATTTTGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAG
GTATTAATTGGAATAGTGGTAGCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAAC
GCCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCCGAGGACACGGCCTTGTATTACTGTGCAAAAGA
TATAGCAGCAGCTGGTGAATTCTACTTCGATATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA

>38B1 VH amino acid sequence (SEQ ID NO:34)

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDFAMHWVRQAPGKGLEWVSGINWNSGSIGYADSVKG
RFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDIAAAGEFYFDMDVWGQGTTVTVSS

>38B1 VL nucleic acid sequence (SEQ ID NO:35)

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGC
CAGTCAGAGTGTTAGCAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG
ATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC
ATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCTCCGACTTTTGG
CCAGGGGACCAAGCTGGAGATCAAA

>38B1 VL amino acid sequence (SEQ ID NO:36)

EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT
ISSLEPEDFAVYYCQQRSNWPPTFGQGTKLEIK

The 15E6 antibody includes a distinct heavy chain variable region (SEQ ID NO:38) encoded by the nucleic acid sequence shown in SEQ ID NO:37, and a light chain variable region (SEQ ID NO:40) encoded by the nucleic acid sequence shown in SEQ ID NO:39

>15E6 VH nucleic acid sequence (SEQ ID NO:37)

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAG
GTATTAATTGGAATAGTGGTGGCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAAC
GCCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAGAGA
TATGGGGGGGTTCGGGGAGTTTTACTGGAACTTCGGTCTCTGGGGCCGTGGCACCCTGGTCACTGTCTCCTCA

>15E6 VH amino acid sequence (SEQ ID NO:38)

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGINWNSGGIGYADSVKGRFTISRDN
AKNSLYLQMNSLRAEDTALYYCARDMGGFGEFYWNFGLWGRGTLVTVSS

>15E6 VL nucleic acid sequence (SEQ ID NO:39)

GAAATTGTGTTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGC
CAGTCAGAGTGTTAGAAGCTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATG
ATGCATCCAACAGGGCCACTGGCATCCCAGCCAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACC
ATCAGCAGCCTAGAGCCTGAAGATTTTGCAGTTTATTACTGTCAGCAGCGTAGCAACTGGCCTCCGGCCACTTT
CGGCGGAGGGACCAAGGTGGAGATCAAA

>15E6 VL amino acid sequence (SEQ ID NO:40)

EIVLTQSPATLSLSPGERATLSCRASQSVRSYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLT
ISSLEPEDFAVYYCQQRSNWPPATFGGGTKVEIK

The 5E12 antibody includes a heavy chain variable region (SEQ ID NO:44) encoded by the nucleic acid sequence shown in SEQ ID NO:43, and a light chain variable region (SEQ ID NO:46) encoded by the nucleic acid sequence shown in SEQ ID NO:45. The 5E12 antibody binds IL-17F and the IL-17F homodimer, but does not bind IL-17A or the IL-17A/IL-17F heterodimeric complex.

>5E12 VH nucleic acid sequence (SEQ ID NO:43)

CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAG
GTATTAGTTGGAATAGTGGTACCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAAC
GCCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAAAGA
ACTGTATATCAGTGACTGGGACTCCTACTCCTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT
CCTCA

>5E12 VH amino acid sequence (SEQ ID NO:44)

QVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGTIGYADSVKGRFTISRDN
AKNSLYLQMNSLRAEDTALYYCAKELYISDWDSYSYGMDVWGQGTTVTVSS

>5E12 VL nucleic acid sequence (SEQ ID NO:45)

GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAAGAGCCACCCTCTCCTGCAGGGC
CAGTCAGAGTGTTAGCAGCAGCTACTTAGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCT
ATGGTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTC
ACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGTAGCTCACCTTTCGGCGG
AGGGACCAAGGTGGAGATCAAA

>5E12 VL amino acid sequence (SEQ ID NO:46)

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFTL
TISRLEPEDFAVYYCQQYGSSPFGGGTKVEIK

The 41B10 antibody includes a heavy chain variable region (SEQ ID NO:48) encoded by the nucleic acid sequence shown in SEQ ID NO:47, and a light chain variable region (SEQ ID NO:50) encoded by the nucleic acid sequence shown in SEQ ID NO:49. The 5E12 antibody binds IL-17F, the IL-17F homodimer, and the IL-17A/IL-17F heterodimeric complex, but does not bind IL-17A.

>41B10 VH nucleic acid sequence (SEQ ID NO:47)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTAAAGCCTGGGGGGTCCCTTAGACTCTCCTGTGCAGCCTC
TGGATTCACTTTCAGTAACGCCTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGGTTGGCC
GTATTAAAAGCAAAACTGATGGTGGGACAACAGACTACGTTGCACCCGTGAAAGGCAGATTCACCATCTCAAGA
GATGATTCAAAAAACACCCTGTATCTGCAAATGAACAGCCTGAAAACCGAGGACACAGCCGTATATTACTGTAC
CACATCGTATAGCAGTTACTGGTTCCCCTACTACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCT
CA

>41B10 VH amino acid sequence (SEQ ID NO:48)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIKSKTDGGTTDYVAPVKGRFTISR
DDSKNTLYLQMNSLKTEDTAVYYCTTSYSSYWFPYYFDYWGQGTLVTVSS

>41B10 VL nucleic acid sequence (SEQ ID NO:49)

GACATCCAGATGACCCAGTCTCCATCCTCACTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGTCGGGC
GAGTCAGGGTATTAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGAGAAAGCCCCTAAGTCCCTGATCTATG
CTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGATTTCACTCTCACC
ATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGCCAACAGTATAATAGTTACCCGATCACCTTCGG
CCAAGGGACACGACTGGAGATTAAA

>41B10 VL amino acid sequence (SEQ ID NO:50)

DIQMTQSPSSLSASVGDRVTITCRASQGISSWLAWYQQKPEKAPKSLIYAASSLQSGVPSRFSGSGSGTDFTLT
ISSLQPEDFATYYCQQYNSYPITFGQGTRLEIK

huIL-17A/F antibodies of the invention additionally comprise, for example, the heavy chain complementarity determining regions (VH CDRs) shown below in Table 1, the light chain complementarity determining regions (VL CDRs) shown in Table 2, and combinations thereof.

Variants of huIL-17F Antibodies

Variants of several of the huIL-17F antibodies described herein were prepared by modifying DNA sequences of parental antibody coding genes. For example, DNA modifications were made to the 30D12 and 15E6 heavy chain variable regions and the 39F12 light chain variable region. Specifically, these amino acid changes resulted in a number of changes in these antibodies. For example, the modifications made to the 30D12 heavy chain variable region resulted in the elimination of a glycosylation site in the 30D12 heavy chain. (N-linked glycosylation sites are NXS or NXT, where X is any amino acid except P). Additionally, modifications made to the 30D12 and 15E6 VH CDRs provided for greater chemical stability and homogeneity of antibody preparation by eliminating (*i.e.*, substituting) residues prone to chemical modifications. For example, in CDR2 of 15E6 VH,

the asparagine residue, capable of forming an isoaspartate, was changed to serine. In 30D12 VH CDR2 and 15E6 VH CDR3, methionine residues were changed to leucine and isoleucine, respectively, in order to eliminate the possibility of methionine sulfur oxidation. Additional modifications to the 30D12 heavy chain variable region and 39F12 light chain variable region restituted the original framework sequences of the human germline (*e.g.*, Asn to Ser in framework 3 of 30D12 VH, and Ala to Thr in framework 3 of 39F12 VL).

The 30D12, 15E6 and 39F12 variants are described herein as 30D12BF, 15E6FK and 39F12A, respectively. The heavy chain variable region (VH) and light chain variable region (VL) for each of these variants are shown in the amino acid and corresponding nucleic acid sequences listed below.

The 30D12BF antibody includes a distinct heavy chain variable region (SEQ ID NO:52) encoded by the nucleic acid sequence shown in SEQ ID NO:51, and shares a light chain variable region with the parent 30D12 antibody (SEQ ID NO:4) encoded by the nucleic acid sequence shown in SEQ ID NO:3. The modified residues in the nucleic acid sequence shown in SEQ ID NO:51 are indicated in bold, underlined and shaded lettering. The CDRs in the amino acid sequence shown in SEQ ID NO:52 are indicated in double-underlined lettering, while the modified residues are un-bolded, italicized and shaded gray.

>30D12BF VH nucleic acid sequence (SEQ ID NO:51)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTCAGTGAAGGTCTCCTGCAAGGCTTC
TGGATACACCTTCACCAGTTATGATATCAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGAT
GGCTGAACCCTGACAGTGGTGTCATACGTTATGCACAGAAGTTCCAGGGTAGAGTCACCATGACCAGGGACACC
TCCATAAGCACAGCCTACATGGAGCTAAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGA
ATGGTTCGGGGAGTTACCCTCTTACTACTTCTACTCCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCG
TCTCCTCA

>30D12BF VH amino acid sequence (SEQ ID NO:52)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWMGWLNPDSGVIRYAQKFQGRVTMTRDT
SISTAYMELSSLRSEDTAVYYCAREWFGELPSYYFYSGMDVWGQGTTVTVSS

In SEQ ID NO:52, Met was changed to Leu to prevent possible methionine sulfur oxidation; The NTS motif was changed to DTS to eliminate a glycosylation site in framework 3; and a backmutation (to germline) of Asn to Ser was introduced in framework 3.

The 15E6FK antibody includes a distinct heavy chain variable region (SEQ ID NO:54) encoded by the nucleic acid sequence shown in SEQ ID NO:53, and shares a light chain variable region with the parent 15E6 antibody (SEQ ID NO:40) encoded by the nucleic acid sequence shown in SEQ ID NO:39. The modified residues in the nucleic acid

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sequence shown in SEQ ID NO:53 are indicated in bold, underlined and shaded lettering. The CDRs in the amino acid sequence shown in SEQ ID NO:54 are indicated in double-underlined lettering, while the modified residues are un-bolded, italicized and shaded gray.

>15E6FK VH nucleic acid sequence (SEQ ID NO:53)

GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTCCCTGAGACTCTCCTGTGCAGCCTC
TGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAG
GTATTAATTGGA**GC**AGTGGTGGCATAGGCTATGCGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAAC
GCCAAGAACTCCCTGTATCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCTTGTATTACTGTGCAAGAGA
TAT**C**GGGGGGTTCGGGGAGTTTTACTGGAACTTCGGTCTCTGGGGCCGTGGCACCCTGGTCACTGTCTCCTCA

>15E6FK VH amino acid sequence (SEQ ID NO:54)

**EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGINWSSGGIGYADSVKGRFTISRDN
AKNSLYLQMNSLRAEDTALYYCARDIGGPGEFYWNFGLWGRGTLVTVSS**

In SEQ ID NO:54, NS was changed to SS in CDR2 to prevent the potential of Asn deamidation, and Met was changed to Ile to prevent the potential for methionine sulfur oxidation.

The 39F12A antibody shares a heavy chain variable region with the parent 39F12 antibody (SEQ ID NO:18) encoded by the nucleic acid sequence shown in SEQ ID NO: 17, and includes a distinct light chain variable region (SEQ ID NO:56) encoded by the nucleic acid sequence shown in SEQ ID NO:55. The modified residues in the nucleic acid sequence shown in SEQ ID NO:55 are indicated in bold, underlined and shaded lettering. The CDRs in the amino acid sequence shown in SEQ ID NO:56 are indicated in double-underlined lettering, while the modified residues are un-bolded, italicized and shaded gray.

>39F12A VL nucleic acid sequence (SEQ ID NO:55)

GAAATTGTGTTGACACAGTCTCCAGACTTTCAGTCTGTGACTCCAAAGGAGAAAGTCACCATCACCTGCCGGGC
CAGTCAGAGCATTGGTAGTAGCTTACACTGGTACCAGCAGAAACCAGATCAGTCTCCAAAGCTCCTCATCAAGT
ATGCTTCCCAGTCCTTCTCAGGGGTCCCCTCGAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACCCTCACC
ATCAATAGCCTGGAAGCTGAAGATGCTGCA**A**CGTATTACTGTCATCAGAGTAGTAGTTTACCGTGGACGTTCGG
CCAAGGGACCAAGGTGGAAATCAAA

>39F12A VL amino acid sequence (SEQ ID NO:56)

**EIVLTQSPDFQSVTPKEKVTITCRASQSIGSSLHWYQQKPDQSPKLLIKYASQSFSGVPSRFSGSGSGTDFTLT
INSLEAEDAA**T**YYC**HQSSSLPWT**FGQGTKVEIK**

In SEQ ID NO:56, a backmutation of Ala to Thr was introduced in framework 3.

Each of these variants additionally comprise, for example, the heavy chain complementarity determining regions (VH CDRs) as shown below in Table 1, the light chain complementarity determining regions (VL CDRs) as shown in Table 2, and combinations thereof. Modifications to VH CDRs in these clones are shown in Table 1 in bold, italicized, and underlined lettering.

Table 1. VH CDR sequences from antibody clones that bind and neutralize huIL-17A/F biological activity

CloneID	Heavy CDR1	Heavy CDR2	Heavy CDR3	Gene family
30D12 IgG1	SYDIN (SEQ ID NO:57)	WMNPDSGVIRYAQKFQG (SEQ ID NO:58)	EWFGELPSYYFYSGMDV (SEQ ID NO:59)	IGHV1-8
29D8 IgG1	TYGIS (SEQ ID NO:60)	WISAYNSNTNYAQKVQG (SEQ ID NO:61)	FFGGHSGYHYGLDV (SEQ ID NO:62)	IGHV1-18
1E4 IgG4	TYGIS (SEQ ID NO:60)	WISVYNGNTNYGQNFQG (SEQ ID NO:63)	FHGGHSGYHYGLDV (SEQ ID NO:64)	IGHV1-18
31A3 IgG1	TYGIS (SEQ ID NO:60)	WITVYNGNTNYAQKFHG (SEQ ID NO:65)	FHGGHSGYHYGLDV (SEQ ID NO:64)	IGHV1-18
4B11 IgG1	SRSYYWG (SEQ ID NO:66)	SIYYSGSTYYNPSLKS (SEQ ID NO:67)	VSGWNGNWFDP (SEQ ID NO:68)	IGHV3-9
39F12 IgG4	SYAFS (SEQ ID NO:69)	GIIPFFGTTNYAQKFQG (SEQ ID NO:70)	DRDYYGLGSPFYYYGMDV (SEQ ID NO:71)	IGHV1-69
12B12 IgG4	SYAFS (SEQ ID NO:69)	GIIPFFGTVNYAQKFQG (SEQ ID NO:72)	DRDYYGLGSPLHYYGLDV (SEQ ID NO:73)	IGHV1-69
15B7 IgG4	SYAFS (SEQ ID NO:69)	GIIPFFGTAHYAQKFQG (SEQ ID NO:74)	DRDYYGSGSPFHFSGLDV (SEQ ID NO:75)	IGHV1-69
4H11 IgG1	GSSMH (SEQ ID NO:76)	RIRSKANSYATAYAASVIG (SEQ ID NO:77)	SVATTLTDYYGMDV (SEQ ID NO:78)	IGHV3-73
8B11 IgG3	SFNMD (SEQ ID NO:79)	SISTTSRIIYSADSVKG (SEQ ID NO:80)	VSYYGHGFDY (SEQ ID NO:81)	IGHV3-48
38B1 IgG1	DFAMH (SEQ ID NO:82)	GINWNSGSIGYADSVKG (SEQ ID NO:83)	DIAAAGEFYFDMDV (SEQ ID NO:84)	IGHV3-9
15E6 IgG4	DYAMH (SEQ ID NO:85)	GINWNSGGIGYADSVKG (SEQ ID NO:86)	DMGGFGEFYWNFGL (SEQ ID NO:87)	IGHV3-9
5E12 IgG4	DYAMH (SEQ ID NO:85)	GISWNSGTIGYADSVKG (SEQ ID NO:88)	ELYISDWDSYSYGMDV (SEQ ID NO:89)	IGHV3-9
41B10 IgG4	NAWMS (SEQ ID NO:90)	RIKSKTDGGTTDYVAPVKG (SEQ ID NO:91)	SYSSYWFPYYFDY (SEQ ID NO:92)	IGHV3-15
30D12BF	SYDIN (SEQ ID NO:57)	W***L***NPDSGVIRYAQKFQG (SEQ ID NO:93)	EWFGELPSYYFYSGMDV (SEQ ID NO:59)	IGHV1-8
15E6FK IgG1	DYAMH (SEQ ID NO:85)	GINW***S***SGGIGYADSVKG (SEQ ID NO:94)	D***I***GGFGEFYWNFGL (SEQ ID NO:95)	IGHV3-9

Table 2. VL CDR sequences from antibody clones that bind and neutralize IL-17F

CloneID	LightCDR1	LightCDR2	LightCDR3	Gene family
30D12	RASQSVSSYLA (SEQ ID NO:96)	DASNRAT (SEQ ID NO:97)	QQRSNWPPT (SEQ ID NO:98)	IGKV3-11, IGKJ3
29D8	RASQSVSSYLA (SEQ ID NO:96)	DASNRAT (SEQ ID NO:97)	QQRSNWPPYT (SEQ ID NO:99)	IGKV3-11
1E4	RASQSVSSYLA (SEQ ID NO:96)	DASNRAT (SEQ ID NO:97)	QQRSNWPPYT (SEQ ID NO:99)	IGKV3-11
31A3	RASQSVSSYLA (SEQ ID NO:96)	DASNRAT (SEQ ID NO:97)	QQRSNWPPYT (SEQ ID NO:99)	IGKV3-11
4H11	RASQSVSSYLA (SEQ ID NO:96)	DASNRAT (SEQ ID NO:97)	QQRSNWPPFT (SEQ ID NO:100)	IGKV3-11
4B11	RASQSVSSSYLA (SEQ ID NO:101)	GASSRAT (SEQ ID NO:102)	QQYGSSPIT (SEQ ID NO:103)	IGKV3-20, IGKJ5
39F12	RASQSIGSSLH (SEQ ID NO:104)	YASQSFS (SEQ ID NO:105)	HQSSSLPWT (SEQ ID NO:106)	IGKV6-21
12B12	RASQSIGSSLH (SEQ ID NO:104)	YASQSFS (SEQ ID NO:105)	HQSSSLPWT (SEQ ID NO:106)	IGKV6-21
15B7	RASQSIGSSLH (SEQ ID NO:104)	YASQSFS (SEQ ID NO:105)	HQSSSLPWT (SEQ ID NO:106)	IGKV6-21
8B11	RASQGISSWLA (SEQ ID NO:107)	AASSLQS (SEQ ID NO:108)	QQYNSYPLT (SEQ ID NO:109)	IGKV1D-16
38B1	RASQSVSSYLA (SEQ ID NO:96)	DASNRAT (SEQ ID NO:97)	QQRSNWPP-T (SEQ ID NO:98)	IGKV3-11, IGKJ2
15E6	RASQSVRSYLA (SEQ ID NO:110)	DASNRAT (SEQ ID NO:97)	QQRSNWPPAT (SEQ ID NO:111)	IGKV3-11, IGKJ4
5E12	RASQSVSSSYLA (SEQ ID NO:101)	GASSRAT (SEQ ID NO:102)	QQYGSSP (SEQ ID NO:112)	IGKV3-20
41B10	RASQGISSWLA (SEQ ID NO:107)	AASSLQS (SEQ ID NO:108)	QQYNSYPIT (SEQ ID NO:113)	IGKV1D-16

The amino acids encompassing the complementarity determining regions (CDR) are as defined by E.A. Kabat et al. (*See* Kabat, EA, *et al.*, Sequences of Protein of immunological interest, Fifth Edition, US Department of Health and Human Services, US Government Printing Office (1991)).

Also included in the invention are antibodies that bind to the same epitope as the antibodies described herein. For example, antibodies of the invention specifically bind to IL-17F, wherein the antibody binds to an epitope that includes one or more amino acid residues on human IL-17F (Accession No. AAH70124). Antibodies of the invention specifically bind to IL-17F and IL-17A when not complexed together, wherein the antibody binds to an epitope that includes one or more amino acid residues on human IL-17F, human

IL-17A (*e.g.*, Accession No. AAH67505), or both. Antibodies of the invention specifically bind IL-17F and the heterodimeric IL-17A/IL-17F complex, wherein the antibody binds to an epitope on human IL-17F (*e.g.*, Accession No. AAH70124) and/or an epitope on human IL-17A (*e.g.*, Accession No. AAH67505). Antibodies of the invention specifically bind to both IL-17F, IL-17A and IL-17A/IL-17F wherein the antibody binds to an epitope on human IL-17F (*e.g.*, Accession No. AAH70124) and/or an epitope on human IL-17A (*e.g.*, Accession No. AAH67505).

Those skilled in the art will recognize that it is possible to determine, without undue experimentation, if a monoclonal antibody (*e.g.*, fully human monoclonal antibody) has the same specificity as a monoclonal antibody of the invention (*e.g.,* clones 30D12, 29D8, 1E4, 31A3, 5E12, 39F12, 12B12, 15B7, 4H11, 41B10, 8B11, 38B1, 15E6, 30D12BF, 15E6FK, and 39F12A) by ascertaining whether the former prevents the latter from binding to IL-17F, IL-17A, and/or the IL-17A/IL-17F complex. If the monoclonal antibody being tested competes with the monoclonal antibody of the invention, as shown by a decrease in binding by the monoclonal antibody of the invention, then the two monoclonal antibodies bind to the same, or a closely related, epitope.

An alternative method for determining whether a monoclonal antibody has the specificity of monoclonal antibody of the invention is to pre-incubate the monoclonal antibody of the invention with soluble IL-17F, IL-17A or IL-17A/IL-17F protein (with which it is normally reactive), and then add the monoclonal antibody being tested to determine if the monoclonal antibody being tested is inhibited in its ability to bind the IL-17F, IL-17A and/or the IL-17A/IL-17F complex. If the monoclonal antibody being tested is inhibited then, in all likelihood, it has the same, or functionally equivalent, epitopic specificity as the monoclonal antibody of the invention.

Screening of monoclonal antibodies of the invention, can be also carried out, *e.g.*, by measuring IL-17F, IL-1A and or IL-17A/IL-17F-induced cytokine and/or chemokine production (*e.g.*, IL-6, IL-8, G-CSF, GM-CSF, GRO-α, GRO-b, LIX, GCP-2, MIG, IP10, I-TAC, ,and MCP-1, RANTES, Eotaxin, SDF-1, and MIP3a) and determining whether the test monoclonal antibody is able to modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with IL-17F, IL-1A and or IL-17F/ IL-17A -induced cytokine and/or chemokine production.

Various procedures known within the art may be used for the production of monoclonal antibodies directed against IL-17F, IL-17A, and/or IL-17A/IL-17F, or against derivatives, fragments, analogs homologs or orthologs thereof. (*See, for example,*

Antibodies: A Laboratory Manual, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference). Fully human antibodies are antibody molecules in which the entire sequence of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies", or "fully human antibodies" herein. Human monoclonal antibodies are prepared, for example, using the procedures described in the Examples provided below. Human monoclonal antibodies can be also prepared by using the trioma technique; the human B-cell hybridoma technique (*see* Kozbor, et al., 1983 Immunol Today 4: 72); and the EBV hybridoma technique to produce human monoclonal antibodies (*see* Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies may be utilized and may be produced by using human hybridomas (*see* Cote, et al., 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus *in vitro* (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

Antibodies are purified by well-known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, may be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

The antibodies of the invention (*e.g.,* 30D12, 29D8, 1E4, 31A3, 5E12, 39F12, 12B12, 15B7, 4H11, 41B10, 8B11, 38B1, 15E6, 30D12BF, 15E6FK, and 39F12A) are fully human monoclonal antibodies. Monoclonal antibodies that modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with pro-inflammatory cytokine production mediated by IL-17F, IL-17A and/or IL-17A/IL-17F are generated, *e.g.*, by immunizing an animal with IL-17F or IL-17A/IL-17F, such as, for example, murine, rat or human IL-17F or IL-17A/IL-17F or an immunogenic fragment, derivative or variant thereof. Alternatively, the animal is immunized with cells transfected with a vector containing a nucleic acid molecule encoding IL-17F or IL-17A/IL-17F, such that IL-17F or IL-17A/IL-17F is expressed and associated with the surface of the transfected cells. Alternatively, the antibodies are obtained by screening a library that contains antibody or antigen binding domain sequences for binding to IL-17F or IL-17A/IL-17F. This library is prepared, *e.g.*, in bacteriophage as protein or peptide fusions to a bacteriophage coat protein that is expressed

on the surface of assembled phage particles and the encoding DNA sequences contained within the phage particles (*i.e.*, "phage displayed library"). Hybridomas resulting from myeloma/B cell fusions are then screened for reactivity to IL-17F, IL-17A and/or IL-17A/IL-17F.

Monoclonal antibodies are prepared, for example, using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized *in vitro*.

The immunizing agent will typically include the protein antigen, a fragment thereof or a fusion protein thereof. Generally, either peripheral blood lymphocytes are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of monoclonal antibodies. (*See* Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al., Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63)).

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980). Moreover, in therapeutic applications of monoclonal antibodies, it is important to identify antibodies having a high degree of specificity and a high binding affinity for the target antigen.

After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. (*See* Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

Monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (*see* U.S. Patent No. 4,816,567; Morrison, Nature 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an

antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

Human Antibodies and Humanization of Antibodies

Monoclonal antibodies of the invention include fully human antibodies or humanized antibodies. These antibodies are suitable for administration to humans without engendering an immune response by the human against the administered immunoglobulin.

A huIL-17A/F antibody is generated, for example, using the procedures described in the Examples provided below.

In other, alternative methods, a huIL-17A/F antibody is developed, for example, using phage-display methods using antibodies containing only human sequences. Such approaches are well-known in the art, *e.g.*, in WO92/01047 and U.S. Pat. No. 6,521,404, which are hereby incorporated by reference. In this approach, a combinatorial library of phage carrying random pairs of light and heavy chains are screened using natural or recombinant source of IL-17F, IL-17A and/or IL-17A/IL-17F or fragments thereof. In another approach, a huIL-17F antibody can be produced by a process wherein at least one step of the process includes immunizing a transgenic, non-human animal with human IL-17F protein. In this approach, some of the endogenous heavy and/or kappa light chain loci of this xenogenic non-human animal have been disabled and are incapable of the rearrangement required to generate genes encoding immunoglobulins in response to an antigen. In addition, at least one human heavy chain locus and at least one human light chain locus have been stably transfected into the animal. Thus, in response to an administered antigen, the human loci rearrange to provide genes encoding human variable regions immunospecific for the antigen. Upon immunization, therefore, the xenomouse produces B-cells that secrete fully human immunoglobulins.

A variety of techniques are well-known in the art for producing xenogenic non-human animals. For example, see U.S. Pat. No. 6,075,181 and No. 6,150,584, which is hereby incorporated by reference in its entirety. This general strategy was demonstrated in connection with generation of the first XenoMouse™ strains as published in 1994. *See* Green *et al.* Nature Genetics 7:13-21 (1994), which is hereby incorporated by reference in its entirety. *See also*, U.S. Patent Nos. 6,162,963, 6,150,584, 6, 114,598, 6,075,181, and 5,939,598 and Japanese Patent Nos. 3 068 180 B2, 3 068 506 B2, and 3 068 507 B2 and European Patent No., EP 0 463 151 B1 and International Patent Applications No. WO 94/02602, WO 96/34096, WO 98/24893, WO 00/76310 and related family members.

In an alternative approach, others have utilized a "minilocus" approach in which an exogenous Ig locus is mimicked through the inclusion of pieces (individual genes) from the Ig locus. Thus, one or more VH genes, one or more D_H genes, one or more J_H genes, a mu constant region, and a second constant region (preferably a gamma constant region) are formed into a construct for insertion into an animal. See *e.g.*, U.S. Patent Nos. 5,545,806; 5,545,807; 5,591,669; 5,612,205;5,625,825; 5,625,126; 5,633,425; 5,643,763; 5,661,016; 5,721,367; 5,770,429; 5,789,215; 5,789,650; 5,814,318; 5,877; 397; 5,874,299; 6,023,010; and 6,255,458; and European Patent No. 0 546 073 B1; and International Patent Application Nos. WO 92/03918, WO 92/22645, WO 92/22647, WO 92/22670, WO 93/12227, WO 94/00569, WO 94/25585, WO 96/14436, WO 97/13852, and WO 98/24884 and related family members.

Generation of human antibodies from mice in which, through microcell fusion, large pieces of chromosomes, or entire chromosomes, have been introduced, has also been demonstrated. *See* European Patent Application Nos. 773 288 and 843 961.

Human anti-mouse antibody (HAMA) responses have led the industry to prepare chimeric or otherwise humanized antibodies. While chimeric antibodies have a human constant region and a immune variable region, it is expected that certain human anti-chimeric antibody (HACA) responses will be observed, particularly in chronic or multi-dose utilizations of the antibody. Thus, it would be desirable to provide fully human antibodies against IL-17F, IL-17A and/or IL-17A/IL-17F in order to vitiate or otherwise mitigate concerns and/or effects of HAMA or HACA response.

The production of antibodies with reduced immunogenicity is also accomplished via humanization, chimerization and display techniques using appropriate libraries. It will be appreciated that murine antibodies or antibodies from other species can be humanized or primatized using techniques well known in the art. *See e.g.,* Winter and Harris Immunol Today 14:43 46 (1993) and Wright *et al.* Crit, Reviews in Immunol. 12125-168 (1992). The antibody of interest may be engineered by recombinant DNA techniques to substitute the CH1, CH2, CH3, hinge domains, and/or the framework domain with the corresponding human sequence (*See* WO 92102190 and U.S. Patent Nos. 5,530,101, 5,585,089, 5, 693,761, 5,693,792, 5,714,350, and 5,777,085). Also, the use of Ig cDNA for construction of chimeric immunoglobulin genes is known in the art (Liu *et al.* P.N.A.S. 84:3439 (1987) and J. Immunol. 139:3521 (1987)). mRNA is isolated from a hybridoma or other cell producing the antibody and used to produce cDNA. The cDNA of interest may be amplified by the polymerase chain reaction using specific primers (U.S. Pat. Nos. 4,683,

195 and 4,683,202). Alternatively, a library is made and screened to isolate the sequence of interest. The DNA sequence encoding the variable region of the antibody is then fused to human constant region sequences. The sequences of human constant regions genes may be found in Kabat *et al.* (1991) Sequences of Proteins of immunological Interest, N.I.H. publication no. 91-3242. Human C region genes are readily available from known clones. The choice of isotype will be guided by the desired effecter functions, such as complement fixation, or activity in antibody-dependent cellular cytotoxicity. Preferred isotypes are IgGl, IgG3 and IgG4. Either of the human light chain constant regions, kappa or lambda, may be used. The chimeric, humanized antibody is then expressed by conventional methods.

Antibody fragments, such as Fv, $F(ab')_2$ and Fab may be prepared by cleavage of the intact protein, *e.g.,* by protease or chemical cleavage. Alternatively, a truncated gene is designed. For example, a chimeric gene encoding a portion of the $F(ab')_2$ fragment would include DNA sequences encoding the CH1 domain and hinge region of the H chain, followed by a translational stop codon to yield the truncated molecule.

Consensus sequences of H and L J regions may be used to design oligonucleotides for use as primers to introduce useful restriction sites into the J region for subsequent linkage of V region segments to human C region segments. C region cDNA can be modified by site directed mutagenesis to place a restriction site at the analogous position in the human sequence.

Expression vectors include plasmids, retroviruses, YACs, EBV derived episomes, and the like. A convenient vector is one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed. In such vectors, splicing usually occurs between the splice donor site in the inserted J region and the splice acceptor site preceding the human C region, and also at the splice regions that occur within the human CH exons. Polyadenylation and transcription termination occur at native chromosomal sites downstream of the coding regions. The resulting chimeric antibody may be joined to any strong promoter, including retroviral LTRs, *e.g.,* SV-40 early promoter, (Okayama *et al.* Mol. Cell. Bio. 3:280 (1983)), Rous sarcoma virus LTR (Gorman *et al.* P.N.A.S. 79:6777 (1982)), and moloney murine leukemia virus LTR (Grosschedl *et al.* Cell 41:885 (1985)). Also, as will be appreciated, native Ig promoters and the like may be used.

Further, human antibodies or antibodies from other species can be generated through display type technologies, including, without limitation, phage display, retroviral display, ribosomal display, and other techniques, using techniques well known in the art and the

resulting molecules can be subjected to additional maturation, such as affinity maturation, as such techniques are well known in the art. Wright *et al.* Crit, Reviews in Immunol. 12125-168 (1992), , Hanes and Plückthun PNAS USA 94:4937-4942 (1997) (ribosomal display), Parmley and Smith Gene 73:305-318 (1988) (phage display), Scott, TIBS, vol. 17:241-245 (1992), Cwirla *et al.* PNAS USA 87:6378-6382 (1990), Russel *et al.* Nucl. Acids Research 21:1081-1085 (1993), Hoganboom *et al.* Immunol. Reviews 130:43-68 (1992), Chiswell and McCafferty TIBTECH; 10:80-8A (1992), and U.S. Patent No. 5,733,743. If display technologies are utilized to produce antibodies that are not human, such antibodies can be humanized as described above.

Using these techniques, antibodies can be generated to IL-17F, IL-17A and/or IL-17A/IL-17F expressing cells, IL-17F itself, forms of IL-17F and/or IL-17A, epitopes or peptides thereof, and expression libraries thereto (*See e.g.,* U.S. Patent No. 5,703,057) which can thereafter be screened as described above for the activities described herein.

The huIL-17A/F antibodies of the invention can be expressed by a vector containing a DNA segment encoding the single chain antibody described above.

These can include vectors, liposomes, naked DNA, adjuvant-assisted DNA. gene gun, catheters, *etc.* Vectors include chemical conjugates such as described in WO 93/64701, which has targeting moiety (*e.g.* a ligand to a cellular surface receptor), and a nucleic acid binding moiety (*e.g.* polylysine), viral vector (*e.g.* a DNA or RNA viral vector), fusion proteins such as described in PCT/US 95/02140 (WO 95/22618) which is a fusion protein containing a target moiety (*e.g.* an antibody specific for a target cell) and a nucleic acid binding moiety (*e.g.* a protamine), plasmids, phage, etc. The vectors can be chromosomal, non-chromosomal or synthetic.

Preferred vectors include viral vectors, fusion proteins and chemical conjugates. Retroviral vectors include moloney murine leukemia viruses. DNA viral vectors are preferred. These vectors include pox vectors such as orthopox or avipox vectors, herpesvirus vectors such as a herpes simplex I virus (HSV) vector (*see* Geller, A. I. et al., J. Neurochem, 64:487 (1995); Lim, F., et al., in DNA Cloning: Mammalian Systems, D. Glover, Ed. (Oxford Univ. Press, Oxford England) (1995); Geller, A. I. et al., Proc Natl. Acad. Sci.: U.S.A. 90:7603 (1993); Geller, A. I., et al., Proc Natl. Acad. Sci USA 87:1149 (1990), Adenovirus Vectors (*see* LeGal LaSalle et al., Science, 259:988 (1993); Davidson, et al., Nat. Genet 3:219 (1993); Yang, et al., J. Virol. 69:2004 (1995) and Adeno-associated Virus Vectors (*see* Kaplitt, M. G.. et al., Nat. Genet. 8:148 (1994).

Pox viral vectors introduce the gene into the cells cytoplasm. Avipox virus vectors result in only a short term expression of the nucleic acid. Adenovirus vectors, adeno-associated virus vectors and herpes simplex virus (HSV) vectors are preferred for introducing the nucleic acid into neural cells. The adenovirus vector results in a shorter term expression (about 2 months) than adeno-associated virus (about 4 months), which in turn is shorter than HSV vectors. The particular vector chosen will depend upon the target cell and the condition being treated. The introduction can be by standard techniques, *e.g.* infection, transfection, transduction or transformation. Examples of modes of gene transfer include *e.g.*, naked DNA, $CaPO_4$ precipitation, DEAE dextran, electroporation, protoplast fusion, lipofection, cell microinjection, and viral vectors.

The vector can be employed to target essentially any desired target cell. For example, stereotaxic injection can be used to direct the vectors (*e.g.* adenovirus, HSV) to a desired location. Additionally, the particles can be delivered by intracerebroventricular (icv) infusion using a minipump infusion system, such as a SynchroMed Infusion System. A method based on bulk flow, termed convection, has also proven effective at delivering large molecules to extended areas of the brain and may be useful in delivering the vector to the target cell. (*See* Bobo et al., Proc. Natl. Acad. Sci. USA 91:2076-2080 (1994); Morrison et al., Am. J. Physiol. 266:292-305 (1994)). Other methods that can be used include catheters, intravenous, parenteral, intraperitoneal and subcutaneous injection, and oral or other known routes of administration.

These vectors can be used to express large quantities of antibodies that can be used in a variety of ways. For example, to detect the presence of IL-17F, IL-17A and or the IL-17A/IL-17F complex in a sample. The antibody can also be used to try to bind to and disrupt IL-17F, IL-17A and/or IL-17A/IL-17F-related signaling.

Techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (*see e.g.*, U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of F_{ab} expression libraries (*see e.g.*, Huse, et al., 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal F_{ab} fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen may be produced by techniques known in the art including, but not limited to: (i) an $F_{(ab')2}$ fragment produced by pepsin digestion of an antibody molecule; (ii) an F_{ab} fragment generated by reducing the disulfide bridges of an $F_{(ab')2}$ fragment; (iii) an F_{ab} fragment

generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) F_v fragments.

The invention also includes F_v, F_{ab}, $F_{ab'}$ and $F_{(ab')2}$ anti-IL-17F fragments or anti-IL-17A/IL-17F complex fragments, single chain anti-IL-17F or anti- IL-17A/IL-17F antibodies, bispecific anti- IL-17F, IL-17A and/or anti- IL-17A/IL-17F antibodies, and heteroconjugate anti- IL-17F, IL-17A and/or anti- IL-17A/IL-17F antibodies.

Bispecific antibodies are antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the IL-17F, IL-17A and/or IL-17A/IL-17F complex. The second binding target is any other antigen, and advantageously is a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker et al., EMBO J., 10:3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology, 121:210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced

with larger side chains (*e.g.* tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (*e.g.* alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (*e.g.* $F(ab')_2$ bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Additionally, Fab' fragments can be directly recovered from E. coli and chemically coupled to form bispecific antibodies. Shalaby et al., J. Exp. Med. 175:217-225 (1992) describe the production of a fully humanized bispecific antibody $F(ab')_2$ molecule. Each Fab' fragment was separately secreted from E. coli and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., J. Immunol. 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., Proc. Natl. Acad. Sci. USA 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody

fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See, Gruber et al., J. Immunol. 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., J. Immunol. 147:60 (1991).

Exemplary bispecific antibodies can bind to two different epitopes, at least one of which originates in the protein antigen of the invention. Alternatively, an anti-antigenic arm of an immunoglobulin molecule can be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (*e.g.* CD2, CD3, CD28, or B7), or Fc receptors for IgG (FcγR), such as FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular antigen. Bispecific antibodies can also be used to direct cytotoxic agents to cells which express a particular antigen. These antibodies possess an antigen-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA. Another bispecific antibody of interest binds the protein antigen described herein and further binds tissue factor (TF).

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (*see* U.S. Patent No. 4,676,980), and for treatment of HIV infection (*see* WO 91/00360; WO 92/200373; EP 03089). It is contemplated that the antibodies can be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

It can be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating diseases and disorders associated with IL-17F, IL-17A and/or IL-17A/IL-17F complex signaling. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing

interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). (*See* Caron et al., J. Exp Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992)). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. (*See* Stevenson et al., Anti-Cancer Drug Design, 3: 219-230 (1989)).

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., Science 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. (*See* WO94/11026).

Those of ordinary skill in the art will recognize that a large variety of possible moieties can be coupled to the resultant antibodies of the invention. (*See, for example*, "Conjugate Vaccines", Contributions to Microbiology and Immunology, J. M. Cruse and R.

E. Lewis, Jr (eds), Carger Press, New York, (1989), the entire contents of which are incorporated herein by reference).

Coupling may be accomplished by any chemical reaction that will bind the two molecules so long as the antibody and the other moiety retain their respective activities. This linkage can include many chemical mechanisms, for instance covalent binding, affinity binding, intercalation, coordinate binding and complexation. The preferred binding is, however, covalent binding. Covalent binding can be achieved either by direct condensation of existing side chains or by the incorporation of external bridging molecules. Many bivalent or polyvalent linking agents are useful in coupling protein molecules, such as the antibodies of the present invention, to other molecules. For example, representative coupling agents can include organic compounds such as thioesters, carbodiimides, succinimide esters, diisocyanates, glutaraldehyde, diazobenzenes and hexamethylene diamines. This listing is not intended to be exhaustive of the various classes of coupling agents known in the art but, rather, is exemplary of the more common coupling agents. (*See* Killen and Lindstrom, Jour. Immun. 133:1335-2549 (1984); Jansen et al., Immunological Reviews 62:185-216 (1982); and Vitetta et al., Science 238:1098 (1987).

Preferred linkers are described in the literature. (*See, for example*, Ramakrishnan, S. et al., Cancer Res. 44:201-208 (1984) describing use of MBS (M-maleimidobenzoyl-N-hydroxysuccinimide ester). *See also*, U.S. Patent No. 5,030,719, describing use of halogenated acetyl hydrazide derivative coupled to an antibody by way of an oligopeptide linker. Particularly preferred linkers include: (i) EDC (1-ethyl-3-(3-dimethylamino-propyl) carbodiimide hydrochloride; (ii) SMPT (4-succinimidyloxycarbonyl-alpha-methyl-alpha-(2-pridyl-dithio)-toluene (Pierce Chem. Co., Cat. (21558G); (iii) SPDP (succinimidyl-6 [3-(2-pyridyldithio) propionamido]hexanoate (Pierce Chem. Co., Cat #21651G); (iv) Sulfo-LC-SPDP (sulfosuccinimidyl 6 [3-(2-pyridyldithio)-propianamide] hexanoate (Pierce Chem. Co. Cat. #2165-G); and (v) sulfo-NHS (N-hydroxysulfo-succinimide: Pierce Chem. Co., Cat. #24510) conjugated to EDC.

The linkers described above contain components that have different attributes, thus leading to conjugates with differing physio-chemical properties. For example, sulfo-NHS esters of alkyl carboxylates are more stable than sulfo-NHS esters of aromatic carboxylates. NHS-ester containing linkers are less soluble than sulfo-NHS esters. Further, the linker SMPT contains a sterically hindered disulfide bond, and can form conjugates with increased stability. Disulfide linkages, are in general, less stable than other linkages because the disulfide linkage is cleaved *in vitro*, resulting in less conjugate available. Sulfo-NHS, in

particular, can enhance the stability of carbodimide couplings. Carbodimide couplings (such as EDC) when used in conjunction with sulfo-NHS, forms esters that are more resistant to hydrolysis than the carbodimide coupling reaction alone.

The antibodies disclosed herein can also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang et al., Proc. Natl Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction.

Use of antibodies against IL-17F, IL-17A and/or the IL-17A/IL-17F complex

It will be appreciated that administration of therapeutic entities in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, PA (1975)), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as Lipofectin™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in treatments and therapies in accordance with the present invention, provided that the active ingredient in the formulation is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. *See* also Baldrick P. "Pharmaceutical excipient development: the need for preclinical guidance." Regul. Toxicol Pharmacol. 32(2):210-8 (2000), Wang W. "Lyophilization and development of solid protein pharmaceuticals." Int. J. Pharm. 203(1-2):1-60 (2000), Charman WN "Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts." J Pharm Sci.89(8):967-78 (2000), Powell *et al.* "Compendium of excipients for parenteral formulations" PDA J

Pharm Sci Technol. 52:238-311 (1998) and the citations therein for additional information related to formulations, excipients and carriers well known to pharmaceutical chemists.

In one embodiment, antibodies of the invention, which include a monoclonal antibody of the invention (*e.g.*, a fully human monoclonal antibody), may be used as therapeutic agents. Such agents will generally be employed to diagnose, prognose, monitor, treat, alleviate, and/or prevent a disease or pathology associated with IL-17F, IL-17A and/or IL-17A/IL-17F signaling in a subject. A therapeutic regimen is carried out by identifying a subject, *e.g.*, a human patient suffering from (or at risk of developing) an inflammatory disease or disorder, using standard methods. An antibody preparation, preferably one having high specificity and high affinity for its target antigen, is administered to the subject and will generally have an effect due to its binding with the target. Administration of the antibody may abrogate or inhibit or interfere with the signaling function of the target (*e.g.*, IL-17F, IL-17A or the IL-17A/IL-17F complex). Administration of the antibody may abrogate or inhibit or interfere with the binding of the target (*e.g.*, IL-17F) with an endogenous ligand (*e.g.*, IL-17R or IL-17RC) to which it naturally binds. For example, the antibody binds to the target and modulates, blocks, inhibits, reduces, antagonizes, neutralizes, or otherwise interferes with IL-17F, IL-17A and/or IL-17A/IL-17F-induced proinflammatory cytokine production.

Diseases or disorders related to IL-17F, IL-17A and/or IL-17A/IL-17F signaling include autoimmune diseases or inflammatory diseases or disorders, including but not limited to rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis chronic obstructive pulmonary disease, and asthma. For example, IL-17A expression has been found to be up-regulated in the synovial tissue of rheumatoid arthritis patients (*see* Khono et al., Mod. Rheumatol. Dec. 20 2007, Epub ahead of print). IL-17F was found to be up-regulated in sputum of cystic fibrosis patients (*see* McAllister et al., J.Immunol. 175: 404-412 (2005)), and in the colon of patients suffering from inflammatory bowel disease (*see* Seiderer et al., Inflamm. Bowel Dis. Dec. 18 2007, Epub. ahead of print). IL-17A/IL-17F has been shown to play a role in the recruitment of airway neutrophilia, suggesting a role in the pathogenesis of respiratory disease (*see* Liang et al., J. Immunol. 179(11): 7791-9 (2007)).

IL-17F and IL-17A have also been shown to be upregulated by IL-21 signaling, suggesting that the pro-inflammatory effects associated with IL-21 signaling are mediated by IL-17F, IL-17A and or IL-17F/IL17A (Wei et al., J Biol Chem. 282(48):34605-10 (2007)). As such, the antibodies of the invention are also useful for diagnosing, prognosing,

monitoring and/or treating disorders diseases mediated by IL-21 signaling, including but not limited to inflammatory/autoimmune disorders such as inflammatory bowel disease, rheumatoid arthritis, transplant rejection, and psoriasis.

Symptoms associated with inflammatory-related disorders include, for example, inflammation, fever, general malaise, fever, pain, often localized to the inflamed area, rapid pulse rate, joint pain or aches (arthralgia), rapid breathing or other abnormal breathing patterns, chills, confusion, disorientation, agitation, dizziness, cough, dyspnea, pulmonary infections, cardiac failure, respiratory failure, edema, weight gain, mucopurulent relapses, cachexia, wheezing, headache, and abdominal symptoms such as, for example, abdominal pain, diarrhea or constipation. Symptoms associated with immune-related disorders include, for example, inflammation, fever, loss of appetite, weight loss, abdominal symptoms such as, for example, abdominal pain, diarrhea or constipation, joint pain or aches (arthralgia), fatigue, rash, anemia, extreme sensitivity to cold (Raynaud's phenomenon), muscle weakness, muscle fatigue, changes in skin or tissue tone, shortness of breath or other abnormal breathing patterns, chest pain or constriction of the chest muscles, abnormal heart rate (*e.g.*, elevated or lowered), light sensitivity, blurry or otherwise abnormal vision, and reduced organ function

A therapeutically effective amount of an antibody of the invention relates generally to the amount needed to achieve a therapeutic objective. As noted above, this may be a binding interaction between the antibody and its target antigen that, in certain cases, interferes with the functioning of the target. The amount required to be administered will furthermore depend on the binding affinity of the antibody for its specific antigen, and will also depend on the rate at which an administered antibody is depleted from the free volume other subject to which it is administered. Common ranges for therapeutically effective dosing of an antibody or antibody fragment of the invention may be, by way of nonlimiting example, from about 0.1 mg/kg body weight to about 50 mg/kg body weight. Common dosing frequencies may range, for example, from twice daily to once a week.

Efficaciousness of treatment is determined in association with any known method for diagnosing or treating the particular inflammatory-related disorder. Alleviation of one or more symptoms of the inflammatory-related disorder indicates that the antibody confers a clinical benefit.

Methods for the screening of antibodies that possess the desired specificity include, but are not limited to, enzyme linked immunosorbent assay (ELISA) and other immunologically mediated techniques known within the art.

In another embodiment, antibodies directed against IL-17F, IL-17A and/or the IL-17F/IL17A complex may be used in methods known within the art relating to the localization and/or quantitation of IL-17F, IL-17A or the IL-17A/IL-17F complex (*e.g.*, for use in measuring levels of the IL-17F, IL-17A, and/or the IL-17A/IL-17F complex within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies specific to IL-17F, IL-17A and/or the IL-17A/IL-17F complex, or derivative, fragment, analog or homolog thereof, that contain the antibody derived antigen binding domain, are utilized as pharmacologically active compounds (referred to hereinafter as "Therapeutics").

In another embodiment, an antibody specific for IL-17F, IL-17A and/or the IL-17A/IL-17F complex can be used to isolate an IL-17F or IL-17A polypeptide, or the IL-17A/IL-17F polypeptide by standard techniques, such as immunoaffinity, chromatography or immunoprecipitation. Antibodies directed against the IL-17F, IL-17A and/or IL-17A/IL-17F protein (or a fragment thereof) can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

In yet another embodiment, an antibody according to the invention can be used as an agent for detecting the presence of IL-17A/IL-17F and/or the IL-17A/IL-17F protein (or a protein fragment thereof) in a sample. In some embodiments, the antibody contains a detectable label. Antibodies are polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, F_{ab}, scFv, or $F_{(ab)2}$) is used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another

reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. Included within the usage of the term "biological sample", therefore, is blood and a fraction or component of blood including blood serum, blood plasma, or lymph. That is, the detection method of the invention can be used to detect an analyte mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of an analyte mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of an analyte protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. *In vitro* techniques for detection of an analyte genomic DNA include Southern hybridizations. Procedures for conducting immunoassays are described, for example in "ELISA: Theory and Practice: Methods in Molecular Biology", Vol. 42, J. R. Crowther (Ed.) Human Press, Totowa, NJ, 1995; "Immunoassay", E. Diamandis and T. Christopoulus, Academic Press, Inc., San Diego, CA, 1996; and "Practice and Theory of Enzyme Immunoassays", P. Tijssen, Elsevier Science Publishers, Amsterdam, 1985. Furthermore, *in vivo* techniques for detection of an analyte protein include introducing into a subject a labeled anti-analyte protein antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

Therapeutic Administration and Formulations of huIL-17A/F antibodies

The antibodies of the invention (also referred to herein as "active compounds"), and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Principles and considerations involved in preparing such compositions, as well as guidance in the choice of components are provided, for example, in Remington's Pharmaceutical Sciences: The Science And Practice Of Pharmacy 19th ed. (Alfonso R. Gennaro, et al., editors) Mack Pub. Co., Easton, Pa. : 1995; Drug Absorption Enhancement : Concepts, Possibilities, Limitations, And Trends, Harwood Academic Publishers, Langhorne, Pa., 1994; and Peptide And Protein Drug Delivery (Advances In Parenteral Sciences, Vol. 4), 1991, M. Dekker, New York.

Such compositions typically comprise the antibody and a pharmaceutically acceptable carrier. Where antibody fragments are used, the smallest inhibitory fragment

that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. (*See, e.g.,* Marasco et al., Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993)).

As used herein, the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (*i.e.,* topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration,

suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth

or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a sustained/controlled release formulations, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

For example, the active ingredients can be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions.

Sustained-release preparations can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters,

hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT ™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods.

The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) and can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

The formulation can also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition can comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

In one embodiment, the active compounds are administered in combination therapy, *i.e.*, combined with other agents, *e.g.*, therapeutic agents, that are useful for treating pathological conditions or disorders, such as autoimmune disorders and inflammatory diseases. The term "in combination" in this context means that the agents are given

substantially contemporaneously, either simultaneously or sequentially. If given sequentially, at the onset of administration of the second compound, the first of the two compounds is preferably still detectable at effective concentrations at the site of treatment.

For example, the combination therapy can include one or more antibodies of the invention coformulated with, and/or coadministered with, one or more additional therapeutic agents, *e.g.*, one or more cytokine and growth factor inhibitors, immunosuppressants, anti-inflammatory agents, metabolic inhibitors, enzyme inhibitors, and/or cytotoxic or cytostatic agents, as described in more detail below. Furthermore, one or more antibodies described herein may be used in combination with two or more of the therapeutic agents described herein. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

Preferred therapeutic agents used in combination with an antibody of the invention are those agents that interfere at different stages in an inflammatory response. In one embodiment, one or more antibodies described herein may be coformulated with, and/or coadministered with, one or more additional agents such as other cytokine or growth factor antagonists (*e.g.*, soluble receptors, peptide inhibitors, small molecules, ligand fusions); or antibodies or antigen binding fragments thereof that bind to other targets (*e.g.*, antibodies that bind to other cytokines or growth factors, their receptors, or other cell surface molecules); and anti-inflammatory cytokines or agonists thereof. Nonlimiting examples of the agents that can be used in combination with the antibodies described herein, include, but are not limited to, antagonists of one or more interleukins (ILs) or their receptors, *e.g.*, antagonists of IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-13, IL-15, IL-16, IL-18, IL-21 and IL-22; antagonists of cytokines or growth factors or their receptors, such as tumor necrosis factor (TNF), LT, EMAP-II, GM-CSF, FGF and PDGF. Antibodies of the invention can also be combined with inhibitors of, *e.g.*, antibodies to, cell surface molecules such as CD2, CD3, CD4, CD8, CD20 (*e.g.*, the CD20 inhibitor rituximab (RITUXAN®)), CD25, CD28, CD30, CD40, CD45, CD69, CD80 (B7.1), CD86 (B7.2), CD90, or their ligands, including CD154 (gp39 or CD4OL), or LFA-1/ICAM-1 and VLA-4/VCAM-1 (Yusuf-Makagiansar et al. (2002) *Med. Res. Rev.* 22:146-67). Preferred antagonists that can be used in combination with the antibodies described herein include antagonists of IL-1, IL-12, TNFα, IL-15, IL-18, and IL-22.

Examples of those agents include IL-12 antagonists, such as chimeric, humanized, human or *in vitro*-generated antibodies (or antigen binding fragments thereof) that bind to

IL-12 (preferably human IL-12), *e.g.*, the antibody disclosed in WO 00/56772; IL-12 receptor inhibitors, *e.g.*, antibodies to human IL-12 receptor; and soluble fragments of the IL-12 receptor, *e.g.*, human IL-12 receptor. Examples of IL-15 antagonists include antibodies (or antigen binding fragments thereof) against IL-15 or its receptor, *e.g.*, chimeric, humanized, human or *in vitro*-generated antibodies to human IL-15 or its receptor, soluble fragments of the IL-15 receptor, and IL-15-binding proteins. Examples of IL-18 antagonists include antibodies, *e.g.*, chimeric, humanized, human or *in vitro*-generated antibodies (or antigen binding fragments thereof), to human IL-18, soluble fragments of the IL-18 receptor, and IL-18 binding proteins (IL-18BP). Examples of IL-1 antagonists include Interleukin-1-converting enzyme (ICE) inhibitors, such as Vx740, IL-1 antagonists, *e.g.*, IL-1RA (anikinra, KINERET™, Amgen), sIL1RII (Immunex), and anti-IL-1 receptor antibodies (or antigen binding fragments thereof).

Examples of TNF antagonists include chimeric, humanized, human or *in vitro*-generated antibodies (or antigen binding fragments thereof) to TNF (*e.g.*, human TNFα), such as (HUMIRA™, D2E7, human TNFα antibody), CDP-571/CDP-870/BAY-10-3356 (humanized anti-TNFα antibody; Celltech/Pharmacia), cA2 (chimeric anti-TNFα antibody; REMICADE®, Centocor); anti-TNF antibody fragments (*e.g.*, CPD870); soluble fragments of the TNF receptors, *e.g.*, p55 or p75 human TNF receptors or derivatives thereof, *e.g.*, 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein, ENBREL™; Immunex), p55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein (LENERCEPT®)); enzyme antagonists, *e.g.*, TNFα converting enzyme (TACE) inhibitors (*e.g.*, an alpha-sulfonyl hydroxamic acid derivative, and N-hydroxyformamide TACE inhibitor GW 3333, -005, or -022); and TNF-bp/s-TNFR (soluble TNF binding protein). Preferred TNF antagonists are soluble fragments of the TNF receptors, *e.g.*, p55 or p75 human TNF receptors or derivatives thereof, *e.g.*, 75 kdTNFR-IgG, and TNFα converting enzyme (TACE) inhibitors.

In other embodiments, the antibodies described herein may be administered in combination with one or more of the following: IL-13 antagonists, *e.g.*, soluble IL-13 receptors (sIL-13) and/or antibodies against IL-13; IL-2 antagonists, *e.g.*, DAB 486-IL-2 and/or DAB 389-IL-2 (IL-2 fusion proteins, Seragen), and/or antibodies to IL-2R, *e.g.*, anti-Tac (humanized anti-IL-2R, Protein Design Labs). Yet another combination includes antibodies of the invention, antagonistic small molecules, and/or inhibitory antibodies in combination with nondepleting anti-CD4 inhibitors (DEC-CE9.1/SB 210396; nondepleting primatized anti-CD4 antibody; IDEC/SmithKline). Yet other preferred combinations include antagonists of the costimulatory pathway CD80 (B7.1) or CD86 (B7.2), including

antibodies, soluble receptors or antagonistic ligands; as well as p-selectin glycoprotein ligand (PSGL), anti-inflammatory cytokines, *e.g.*, IL-4 (DNAX/Schering); IL-10 (SCH 52000; recombinant IL-10 DNAX/Schering); IL-13 and TGF-β, and agonists thereof (*e.g.*, agonist antibodies).

In other embodiments, one or more antibodies of the invention can be coformulated with, and/or coadministered with, one or more anti-inflammatory drugs, immunosuppressants, or metabolic or enzymatic inhibitors. Nonlimiting examples of the drugs or inhibitors that can be used in combination with the antibodies described herein, include, but are not limited to, one or more of: nonsteroidal anti-inflammatory drug(s) (NSAIDs), *e.g.*, ibuprofen, tenidap, naproxen, meloxicam, piroxicam, diclofenac, and indomethacin; sulfasalazine; corticosteroids such. as prednisolone; cytokine suppressive anti-inflammatory drug(s) (CSAIDs); inhibitors of nucleotide biosynthesis, *e.g.*, inhibitors of purine biosynthesis, folate antagonists (*e.g.*, methotrexate (N-[4-[[(2,4-diamino-6-pteridinyl)methyl] methylamino] benzoyl]-L-glutamic acid); and inhibitors of pyrimidine biosynthesis, *e.g.*, dihydroorotate dehydrogenase (DHODH) inhibitors. Preferred therapeutic agents for use in combination with the antibodies of the invention include NSAIDs, CSAIDs, (DHODH) inhibitors (*e.g.*, leflunomide), and folate antagonists (*e.g.*, methotrexate).

Examples of additional inhibitors include one or more of: corticosteroids (oral, inhaled and local injection); immunosuppresants, *e.g.*, cyclosporin, tacrolimus (FK-506); and mTOR inhibitors, *e.g.*, sirolimus (rapamycin - RAPAMUNE™ or rapamycin derivatives, *e.g.*, soluble rapamycin derivatives (*e.g.*, ester rapamycin derivatives, *e.g.*, CCI-779); agents which interfere with signaling by proinflammatory cytokines such as TNFα or IL-1 (*e.g.* IRAK, NIK, IKK, p38 or MAP kinase inhibitors); COX2 inhibitors, *e.g.*, celecoxib, rofecoxib, and variants thereof; phosphodiesterase inhibitors, *e.g.*, R973401 (phosphodiesterase Type IV inhibitor); phospholipase inhibitors, *e.g.*, inhibitors of cytosolic phospholipase 2 (cPLA2) (*e.g.*, trifluoromethyl ketone analogs); inhibitors of vascular endothelial cell growth factor or growth factor receptor, *e.g.*, VEGF inhibitor and/or VEGF-R inhibitor; and inhibitors of angiogenesis. Preferred therapeutic agents for use in combination with the antibodies of the invention are immunosuppresants, *e.g.*, cyclosporin, tacrolimus (FK-506); mTOR inhibitors, *e.g.*, sirolimus (rapamycin) or rapamycin derivatives, *e.g.*, soluble rapamycin derivatives (*e.g.*, ester rapamycin derivatives, *e.g.*, CCI-779); COX2 inhibitors, *e.g.*, celecoxib and variants thereof; and phospholipase inhibitors, *e.g.*, inhibitors of cytosolic phospholipase 2 (cPLA2), *e.g.*, trifluoromethyl ketone analogs.

Additional examples of therapeutic agents that can be combined with an antibody of the invention include one or more of: 6-mercaptopurines (6-MP); azathioprine sulphasalazine; mesalazine; olsalazine; chloroquine/ hydroxychloroquine (PLAQUENIL®); pencillamine; aurothiornalate (intramuscular and oral); azathioprine; coichicine; beta-2 adrenoreceptor agonists (salbutamol, terbutaline, salmeteral); xanthines (theophylline, arninophylline); cromoglycate; nedocromil; ketotifen; ipratropium and oxitropium; mycophenolate mofetil; adenosine agonists; antithrombotic agents; complement inhibitors; and adrenergic agents.

Nonlimiting examples of agents for treating or preventing arthritic disorders (*e.g.*, rheumatoid arthritis, inflammatory arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis and psoriatic arthritis), with which an antibody of the invention may be combined include one or more of the following: IL-12 antagonists as described herein; NSAIDs; CSAIDs; TNFs, *e.g.*, TNFα, antagonists as described herein; nondepleting anti-CD4 antibodies as described herein; IL-2 antagonists as described herein; anti-inflammatory cytokines, *e.g.*, IL-4, IL-10, IL-13 and TGFα, or agonists thereof; IL-1 or IL-1 receptor antagonists as described herein; phosphodiesterase inhibitors as described herein; Cox-2 inhibitors as described herein; iloprost: methotrexate; thalidomide and thalidomide-related drugs (*e.g.*, Celgen); leflunomide; inhibitor of plasminogen activation, *e.g.*, tranexamic acid; cytokine inhibitor, *e.g.*, T-614; prostaglandin El; azathioprine; an inhibitor of interleukin-1 converting enzyme (ICE); zap-70 and/or lck inhibitor (inhibitor of the tyrosine kinase zap-70 or lck); an inhibitor of vascular endothelial cell growth factor or vascular endothelial cell growth factor receptor as described herein; an inhibitor of angiogenesis as described herein; corticosteroid anti-inflammatory drugs (*e.g.*, SB203580); TNF-convertase inhibitors; IL-11; IL-13; IL-17 inhibitors; gold; penicillamine; chloroquine; hydroxychloroquine; chlorambucil; cyclophosphamide; cyclosporine; total lymphoid irradiation; antithymocyte globulin; CD5-toxins; orally administered peptides and collagen; lobenzarit disodium; cytokine regulating agents (CRAs) HP228 and HP466 (Houghten Pharmaceuticals, Inc.); ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); prednisone; orgotein; glycosaminoglycan polysulphate; minocycline (MINOCIN®); anti-IL2R antibodies; marine and botanical lipids (fish and plant seed fatty acids); auranofm; phenylbutazone; meclofenamic acid; flufenamic acid; intravenous immune globulin; zileuton; mycophenolic acid (RS-61443); tacrolimus (FK-506); sirolimus (rapamycin); amiprilose (therafectin); cladribine (2-chlorodeoxyadenosine); and azaribine. Preferred

combinations include one or more antibodies of the invention in combination with methotrexate or leflunomide, and in moderate or severe rheumatoid arthritis cases, cyclosporine.

Preferred examples of inhibitors to use in combination with antibodies of the invention to treat arthritic disorders include TNF antagonists (*e.g.*, chimeric, humanized, human or *in vitro*-generated antibodies, or antigen binding fragments thereof, that bind to TNF; soluble fragments of a TNF receptor, *e.g.*, p55 or p75 human TNF receptor or derivatives thereof, *e.g.*, 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein,. ENBREL™), p55 kD TNF receptor-IgG fusion protein; TNF enzyme antagonists, *e.g.*, TNFα converting enzyme (TACE) inhibitors); antagonists of IL-12, IL-15, IL-18, IL-22; T cell and B cell-depleting agents (*e.g.*, anti-CD4 or anti-CD22 antibodies); small molecule inhibitors, *e.g.*, methotrexate and leflunomide; sirolimus (rapamycin) and analogs thereof, *e.g.*, CCI-779; cox-2 and cPLA2 inhibitors; NSAIDs; p38 inhibitors, TPL-2, Mk-2 and NFkb inhibitors; RAGE or soluble RAGE; P-selectin or PSGL-1 inhibitors (*e.g.*, small molecule inhibitors, antibodies thereto, *e.g.*, antibodies to P-selectin); estrogen receptor beta (ERB) agonists or ERB-NFkb antagonists. Most preferred additional therapeutic agents that can be coadministered and/or coformulated with one or more antibodies of the invention include one or more of: a soluble fragment of a TNF receptor, *e.g.*, p55 or p75 human TNF receptor or derivatives thereof, *e.g.*, 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein, ENBREL™); methotrexate, leflunomide, or a sirolimus (rapamycin) or an analog thereof, *e.g.*, CCI-779.

Nonlimiting examples of agents for treating or preventing multiple sclerosis with which antibodies of the invention can be combined include the following: interferons, *e.g.*, interferon-alphal a (*e.g.*, AVONEX™; Biogen) and interferon-lb (BETASERON™ Chiron/Berlex); Copolymer 1 (Cop-1; COPAXONE™ Teva Pharmaceutical Industries, Inc.); hyperbaric oxygen; intravenous immunoglobulin; cladribine; TNF antagonists as described herein; corticosteroids; prednisolone; methylprednisolone; azathioprine; cyclophosphamide; cyclosporine; cyclosporine A, methotrexate; 4- aminopyridine; and tizanidine. Additional antagonists that can be used in combination with antibodies of the invention include antibodies to or antagonists of other human cytokines or growth factors, for example, TNF, LT, IL-1, IL-2, IL-6, EL-7, IL-8, IL-12 IL-15, IL-16, IL-18, EMAP-11, GM-CSF, FGF, and PDGF. Antibodies as described herein can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD80, CD86, CD90 or their ligands. The antibodies of the invention

may also be combined with agents, such as methotrexate, cyclosporine, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signaling by proinflammatory cytokines as described herein, IL-Ib converting enzyme inhibitors (*e.g.*, Vx740), anti-P7s, PSGL, TACE inhibitors, T-cell signaling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, azathloprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof, as described herein, and anti-inflammatory cytokines (*e.g.* IL-4, IL- 10, IL-13 and TGF).

Preferred examples of therapeutic agents for multiple sclerosis with which the antibodies of the invention can be combined include interferon-β, for example, IFNβ-1a and IFNβ-1b; copaxone, corticosteroids, IL- 1 inhibitors, TNF inhibitors, antibodies to CD40 ligand and CD80, IL-12 antagonists.

Nonlimiting examples of agents for treating or preventing inflammatory bowel disease (*e.g.*, Crohn's disease, ulcerative colitis) with which an antibody of the invention can be combined include the following: budenoside; epidermal growth factor; corticosteroids; cyclosporine; sulfasalazine; aminosalicylates; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitors; mesalamine; olsalazine; balsalazide; antioxidants; thromboxane inhibitors; IL-1 receptor antagonists; anti-IL-1 monoclonal antibodies; anti-IL-6 monoclonal antibodies; growth factors; elastase inhibitors; pyridinyl-imidazole compounds; TNF antagonists as described herein; IL-4, IL-10, IL-13 and/or TGFβ cytokines or agonists thereof (*e.g.*, agonist antibodies); IL-11; glucuronide- or dextran-conjugated prodrugs of prednisolone, dexamethasone or budesonide; ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); slow-release mesalazine; methotrexate; antagonists of platelet activating factor (PAF); ciprofloxacin; and lignocaine.

Nonlimiting examples of agents for treating or preventing psoriasis with which an antibody of the invention can be combined include the following: corticosteroids; vitamin D_3 and analogs thereof; retinoiods (*e.g.*, soriatane); methotrexate; cyclosporine, 6-thioguanine; Accutane; hydrea; hydroxyurea; sulfasalazine; mycophenolate mofetil; azathioprine; tacrolimus; fumaric acid esters;biologics such as Amevive, Enbrel,Humira, Raptiva and Remicade, Ustekinmab, and XP-828L; phototherapy; and photochemotherapy (*e.g.*, psoralen and ultraviolet phototherapy combined).

Nonlimiting examples of agents for treating or preventing inflammatory airway/respiratory disease (*e.g.*, chronic obstructive pulmonary disorder, asthma) with which an antibody of the invention can be combined include the following: beta2-adrenoceptor agonists (*e.g.*, salbutamol (albuterol USAN), levalbuterol, terbutaline, bitolterol); long-acting beta2-adrenoceptor agonists (*e.g.*, salmeterol, formoterol, bambuterol); adrenergic agonists (*e.g.*, inhaled epinephrine and ephedrine tablets); anticholinergic medications (*e.g.*, ipratropium bromide); Combinations of inhaled steroids and long-acting bronchodilators (*e.g.*, fluticasone/salmeterol (Advair in the United States, and Seretide in the United Kingdom)) or. budesonide/formoterol (Symbicort)); inhaled glucocorticoids (*e.g.*, ciclesonide, beclomethasone, budesonide, flunisolide, fluticasone, mometasone, triamcinolone); leukotriene modifiers (*e.g.*, montelukast, zafirlukast, pranlukast, and zileuton); mast cell stabilizers (*e.g.*, cromoglicate (cromolyn), and nedocromil); antimuscarinics/anticholinergics (*e.g.*, ipratropium, oxitropium, tiotropium); methylxanthines (*e.g.*, theophylline, aminophylline); antihistamines; IgE blockers (*e.g.*, Omalizumab); M_3 muscarinic antagonists (anticholinergics) (*e.g.*, ipratropium, tiotropium); cromones (*e.g.*, chromoglicate, nedocromil); zanthines (*e.g.*, theophylline); and TNF antagonists (*e.g.*, infliximab, adalimumab and etanercept).

In one embodiment, an antibody of the invention can be used in combination with one or more antibodies directed at other targets involved in regulating immune responses, *e.g.*, transplant rejection.

Nonlimiting examples of agents for treating or preventing immune responses with which an antibody of the invention can be combined include the following: antibodies against other cell surface molecules, including but not limited to CD25 (interleukin-2 receptor-a), CD11a (LFA-1), CD54 (ICAM-1), CD4, CD45, CD28/CTLA4 (CD80 (B7.1), *e.g.*, CTLA4 Ig - abatacept (ORENCIA®)), ICOSL, ICOS and/or CD86 (B7.2). In yet another embodiment, an antibody of the invention is used in combination with one or more general immunosuppressive agents, such as cyclosporin A or FK506.

In other embodiments, antibodies are used as vaccine adjuvants against autoimmune disorders, inflammatory diseases, etc. The combination of adjuvants for treatment of these types of disorders are suitable for use in combination with a wide variety of antigens from targeted self-antigens, *i.e.*, autoantigens, involved in autoimmunity, *e.g.*, myelin basic protein; inflammatory self-antigens, *e.g.*, amyloid peptide protein, or transplant antigens, *e.g.*, alloantigens. The antigen may comprise peptides or polypeptides derived from proteins, as well as fragments of any of the following: saccharides, proteins, polynucleotides

or oligonucleotides, autoantigens, amyloid peptide protein, transplant antigens, allergens, or other macromolecular components. In some instances, more than one antigen is included in the antigenic composition.

For example, desirable vaccines for moderating responses to allergens in a vertebrate host, which contain the adjuvant combinations of this invention, include those containing an allergen or fragment thereof. Examples of such allergens are described in U.S. Patent No. 5,830,877 and published International Patent Application No. WO 99/51259, which are hereby incorporated by reference in their entireties, and include pollen, insect venoms, animal dander, fungal spores and drugs (such as penicillin). The vaccines interfere with the production of IgE antibodies, a known cause of allergic reactions. In another example, desirable vaccines for preventing or treating disease characterized by amyloid deposition in a vertebrate host, which contain the adjuvant combinations of this invention, include those containing portions of amyloid peptide protein (APP). This disease is referred to variously as Alzheimer's disease, amyloidosis or amyloidogenic disease. Thus, the vaccines of this invention include the adjuvant combinations of this invention plus Aβ peptide, as well as fragments of Aβ peptide and antibodies to Aβ peptide or fragments thereof.

Design and Generation of Other Therapeutics

In accordance with the present invention and based on the activity of the antibodies that are produced and characterized herein with respect to IL-17F, IL-17A and/or IL-17A/IL-17F, the design of other therapeutic modalities beyond antibody moieties is facilitated. Such modalities include, without limitation, advanced antibody therapeutics, such as bispecific antibodies, immunotoxins, and radiolabeled therapeutics, generation of peptide therapeutics, gene therapies, particularly intrabodies, antisense therapeutics, and small molecules.

For example, in connection with bispecific antibodies, bispecific antibodies can be generated that comprise (i) two antibodies one with a specificity to IL-17F, IL-17A and/or IL-17A/IL-17F and another to a second molecule that are conjugated together, (ii) a single antibody that has one chain specific to IL-17F, IL-17A and/or IL-17A/IL-17F and a second chain specific to a second molecule, or (iii) a single chain antibody that has specificity to IL-17F, IL-17A and/or IL-17A/IL-17F and a second molecule. Such bispecific antibodies are generated using techniques that are well known for example, in connection with (i) and (ii) *See e.g.,* Fanger *et al.* Immunol Methods 4:72-81 (1994) and Wright *et al.* Crit, Reviews

in Immunol. 12125-168 (1992), and in connection with (iii) *See e.g.,* Traunecker *et al.* Int. J. Cancer (Suppl.) 7:51-52 (1992).

In connection with immunotoxins, antibodies can be modified to act as immunotoxins utilizing techniques that are well known in the art. *See e.g.,* Vitetta Immunol Today 14:252 (1993). *See* also U.S. Patent No. 5,194,594. In connection with the preparation of radiolabeled antibodies, such modified antibodies can also be readily prepared utilizing techniques that are well known in the art. *See e.g.,* Junghans *et al.* in Cancer Chemotherapy and Biotherapy 655-686 (2d edition, Chafner and Longo, eds., Lippincott Raven (1996)). *See* also U.S. Patent Nos. 4,681,581, 4,735,210, 5,101,827, 5,102,990 (RE 35,500), 5,648,471, and 5,697,902. Each of immunotoxins and radiolabeled molecules would be likely to kill cells expressing IL-17F, IL-17A and/or IL-17A/IL-17F.

In connection with the generation of therapeutic peptides, through the utilization of structural information related to IL-17F, IL-17A and/or IL-17A/IL-17F and antibodies thereto, such as the antibodies of the invention or screening of peptide libraries, therapeutic peptides can be generated that are directed against IL-17F, IL-17A and/or IL-17A/IL-17F. Design and screening of peptide therapeutics is discussed in connection with Houghten *et al.* Biotechniques 13:412-421 (1992), Houghten PNAS USA 82:5131-5135 (1985), Pinalla *et al.* Biotechniques 13:901-905 (1992), Blake and Litzi-Davis BioConjugate Chem. 3:510-513 (1992). Immunotoxins and radiolabeled molecules can also be prepared, and in a similar manner, in connection with peptidic moieties as discussed above in connection with antibodies. Assuming that the IL-17F, IL-17A and/or IL-17A/IL-17F molecule (or a form, such as a splice variant or alternate form) is functionally active in a disease process, it will also be possible to design gene and antisense therapeutics thereto through conventional techniques. Such modalities can be utilized for modulating the function of IL-17F, IL-17A and/or IL-17A/IL-17F. In connection therewith the antibodies of the present invention facilitate design and use of functional assays related thereto. A design and strategy for antisense therapeutics is discussed in detail in International Patent Application No. WO 94/29444. Design and strategies for gene therapy are well known. However, in particular, the use of gene therapeutic techniques involving intrabodies could prove to be particularly advantageous. *See e.g.,* Chen *et al.* Human Gene Therapy 5:595-601 (1994) and Marasco Gene Therapy 4:11-15 (1997). General design of and considerations related to gene therapeutics is also discussed in International Patent Application No. WO 97/38137.

Knowledge gleaned from the structure of the IL-17F, IL-17A and/or IL-17A/IL-17F molecule and its interactions with other molecules in accordance with the present invention,

such as the antibodies of the invention, and others can be utilized to rationally design additional therapeutic modalities. In this regard, rational drug design techniques such as X-ray crystallography, computer-aided (or assisted) molecular modeling (CAMM), quantitative or qualitative structure-activity relationship (QSAR), and similar technologies can be utilized to focus drug discovery efforts. Rational design allows prediction of protein or synthetic structures which can interact with the molecule or specific forms thereof which can be used to modify or modulate the activity of IL-17F, IL-17A and/or IL-17A/IL-17F. Such structures can be synthesized chemically or expressed in biological systems. This approach has been reviewed in Capsey *et al.* Genetically Engineered Human Therapeutic Drugs (Stockton Press, NY (1988)). Further, combinatorial libraries can be designed and synthesized and used in screening programs, such as high throughput screening efforts.

Screening Methods

The invention provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) that modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with binding of the IL-17, IL-17A and/or the IL-17A/IL-17F complex to their innate receptor, or candidate or test compounds or agents that modulate, block, inhibit, reduce, antagonize, neutralize or otherwise interfere with the signaling function of IL-17, IL-17A and/or the IL-17A/IL-17F complex. Also provided are methods of identifying compounds useful to treat disorders associated with IL-17, IL-17A and/or IL-17A/IL-17F signaling. The invention also includes compounds identified in the screening assays described herein.

In one embodiment, the invention provides assays for screening candidate or test compounds which modulate the signaling function of IL-17, IL-17A and/or IL-17A/IL-17F. The test compounds of the invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds. (*See, e.g.,* Lam, 1997. Anticancer Drug Design 12: 145).

A "small molecule" as used herein, is meant to refer to a composition that has a molecular weight of less than about 5 kD and most preferably less than about 4 kD. Small molecules can be, *e.g.*, nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates, lipids or other organic or inorganic molecules. Libraries of chemical and/or biological mixtures, such as fungal, bacterial, or algal extracts, are known in the art and can be screened with any of the assays of the invention.

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt, et al., 1993. Proc. Natl. Acad. Sci. U.S.A. 90: 6909; Erb, et al., 1994. Proc. Natl. Acad. Sci. U.S.A. 91: 11422; Zuckermann, et al., 1994. J. Med. Chem. 37: 2678; Cho, et al., 1993. Science 261: 1303; Carrell, et al., 1994. Angew. Chem. Int. Ed. Engl. 33: 2059; Carell, et al., 1994. Angew. Chem. Int. Ed. Engl. 33: 2061; and Gallop, et al., 1994. J. Med. Chem. 37: 1233.

Libraries of compounds may be presented in solution (*see e.g.*, Houghten, 1992. Biotechniques 13: 412-421), or on beads (*see* Lam, 1991. Nature 354: 82-84), on chips (*see* Fodor, 1993. Nature 364: 555-556), bacteria (*see* U.S. Patent No. 5,223,409), spores (*see* U.S. Patent 5,233,409), plasmids (*see* Cull, et al., 1992. Proc. Natl. Acad. Sci. USA 89: 1865-1869) or on phage (*see* Scott and Smith, 1990. Science 249: 386-390; Devlin, 1990. Science 249: 404-406; Cwirla, *et al.*, 1990. Proc. Natl. Acad. Sci. U.S.A. 87: 6378-6382; Felici, 1991. J. Mol. Biol. 222: 301-310; and U.S. Patent No. 5,233,409.).

In one embodiment, a candidate compound is introduced to an antibody-antigen complex and determining whether the candidate compound disrupts the antibody-antigen complex, wherein a disruption of this complex indicates that the candidate compound modulates the signaling function of IL-17, IL-17A and/or the IL-17A/IL-17F complex. For example, the antibody is monoclonal antibody 5E12 ("Mab05") and the antigen is IL-17F, or the antibody is monoclonal antibody 41B10 and the antigen is IL-17F or IL-17A/IL-17F. Alternatively, the monoclonal antibody is 30D12, 29D8, 1E4, 31A3, 39F12, 12B12, 15B7, 4H11, 4B11, 8B11, 38B1, 15E6, 30D12BF, 15E6FK, or 39F12A and the antigen is the IL-17F, IL-17A or the IL-17A/IL-17F complex.

In another embodiment, the IL-17A/IL-17F complex is provided and exposed to at least one neutralizing monoclonal antibody. Formation of an antibody-antigen complex is detected, and one or more candidate compounds are introduced to the complex. If the antibody-antigen complex is disrupted following introduction of the one or more candidate compounds, the candidate compounds is useful to treat disorders associated with IL-17F, IL-17A and or IL-17A/IL-17F signaling.

In another embodiment, a soluble protein of the invention is provided and exposed to at least one neutralizing monoclonal antibody. Formation of an antibody-antigen complex is detected, and one or more candidate compounds are introduced to the complex. If the antibody-antigen complex is disrupted following introduction of the one or more candidate compounds, the candidate compounds is useful to treat disorders associated with IL-17F, IL-17A and or IL-17A/IL-17F signaling.

Determining the ability of the test compound to interfere with or disrupt the antibody-antigen complex can be accomplished, for example, by coupling the test compound with a radioisotope or enzymatic label such that binding of the test compound to the antigen or biologically-active portion thereof can be determined by detecting the labeled compound in a complex. For example, test compounds can be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, test compounds can be enzymatically-labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In one embodiment, the assay comprises contacting an antibody-antigen complex with a test compound, and determining the ability of the test compound to interact with the antigen or otherwise disrupt the existing antibody-antigen complex. In this embodiment, determining the ability of the test compound to interact with the antigen and/or disrupt the antibody-antigen complex comprises determining the ability of the test compound to preferentially bind to the antigen or a biologically-active portion thereof, as compared to the antibody.

In another embodiment, the assay comprises contacting an antibody-antigen complex with a test compound and determining the ability of the test compound to modulate the antibody-antigen complex. Determining the ability of the test compound to modulate the antibody-antigen complex can be accomplished, for example, by determining the ability of the antigen to bind to or interact with the antibody, in the presence of the test compound.

Those skilled in the art will recognize that, in any of the screening methods disclosed herein, the antibody may be a neutralizing antibody, such as monoclonal antibody 30D12, 29D8, 1E4, 31A3, 4B11, 39F12, 12B12, 15B7, 4H11, 8B11, 38B1, 15E6, 30D12BF, 15E6FK, or 39F12A, each of which modulates or otherwise interferes with proinflammatory cytokine production.

The screening methods disclosed herein may be performed as a cell-based assay or as a cell-free assay. The cell-free assays of the invention are amenable to use soluble IL-17F, IL-17A, and or IL-17A/IL-17F, and fragments thereof.

In more than one embodiment, it may be desirable to immobilize either the antibody or the antigen to facilitate separation of complexed from uncomplexed forms of one or both following introduction of the candidate compound, as well as to accommodate automation of the assay. Observation of the antibody-antigen complex in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided that adds a domain that allows one or both of the proteins to be bound to a matrix. For example, GST-antibody fusion proteins or GST-antigen fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, that are then combined with the test compound, and the mixture is incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined either directly or indirectly. Alternatively, the complexes can be dissociated from the matrix, and the level of antibody-antigen complex formation can be determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either the antibody (*e.g.* 30D12, 29D8, 1E4, 31A3, 39F12, 12B12, 15B7, 4H11, 4B11, 8B11, 38B1, 15E6, 30D12BF, 15E6FK or 39F12A) or the antigen (*e.g.* the IL-17F, IL-17A or IL-17A/IL-17F protein) can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated antibody or antigen molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques well-known within the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, Ill.), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, other antibodies reactive with the antibody or antigen of interest, but which do not interfere with the formation of the antibody-antigen complex of interest, can be derivatized to the wells of the plate, and unbound antibody or antigen trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using such other antibodies reactive with the antibody or antigen.

The invention further pertains to novel agents identified by any of the aforementioned screening assays and uses thereof for treatments as described herein.

Diagnostic and Prophylactic Formulations

The huIL-17A/F MAbs of the invention are used in diagnostic and prophylactic formulations. In one embodiment, an IL-17F, IL-17A and/or IL-17A/IL-17F antagonist, such as a huIL-17A/F MAb of the invention, is administered to patients that are at risk of developing one or more of the aforementioned autoimmune or inflammatory diseases, such as for example, without limitation, rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis chronic obstructive pulmonary disease, asthma, angiogenesis and cancer. A patient's or organ's predisposition to one or more of the aforementioned autoimmune, inflammatory and cell proliferation disorders can be determined using genotypic, serological or biochemical markers.

In another embodiment of the invention, an IL-17F, IL-17A and/or IL-17A/IL-17F antagonist, such as a huIL-17A/F antibody is administered to human individuals diagnosed with a clinical indication associated with one or more of the aforementioned autoimmune or inflammatory diseases such as rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis chronic obstructive pulmonary disease, asthma, angiogenesis and cancer. Upon diagnosis, an IL-17F, IL-17A and/or IL-17A/IL-17F antagonist, such as a huIL-17A/F antibody is administered to mitigate or reverse the effects of the clinical indication associated with rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis chronic obstructive pulmonary disease, asthma, angiogenesis and cancer.

Antibodies of the invention are also useful in the detection of IL-17F, IL-17A and/or IL-17A/IL-17F in patient samples and accordingly are useful as diagnostics. For example, the huIL-17A/F antibodies of the invention are used in *in vitro* assays, *e.g.*, ELISA, to detect IL-17F, IL-17A and/or IL-17A/IL-17F levels in a patient sample.

In one embodiment, a huIL-17A/F antibody of the invention is immobilized on a solid support (*e.g.*, the well(s) of a microtiter plate). The immobilized antibody serves as a capture antibody for any IL-17F, IL-17A and/or IL-17A/IL-17F that may be present in a test sample. Prior to contacting the immobilized antibody with a patient sample, the solid support is rinsed and treated with a blocking agent such as milk protein or albumin to prevent nonspecific adsorption of the analyte.

Subsequently the wells are treated with a test sample suspected of containing the antigen, or with a solution containing a standard amount of the antigen. Such a sample is,

e.g., a serum sample from a subject suspected of having levels of circulating antigen considered to be diagnostic of a pathology. After rinsing away the test sample or standard, the solid support is treated with a second antibody that is detectably labeled. The labeled second antibody serves as a detecting antibody. The level of detectable label is measured, and the concentration of IL-17F, IL-17A and/or IL-17A/IL-17F antigen in the test sample is determined by comparison with a standard curve developed from the standard samples.

It will be appreciated that based on the results obtained using the huIL-17A/F antibodies of the invention in an *in vitro* diagnostic assay, it is possible to stage a disease (*e.g.*, a clinical indication associated with ischemia, an autoimmune or inflammatory disorder) in a subject based on expression levels of the IL-17F, IL-17A and/or IL-17A/IL-17F antigen. For a given disease, samples of blood are taken from subjects diagnosed as being at various stages in the progression of the disease, and/or at various points in the therapeutic treatment of the disease. Using a population of samples that provides statistically significant results for each stage of progression or therapy, a range of concentrations of the antigen that may be considered characteristic of each stage is designated.

All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

EXAMPLES.

EXAMPLE 1: Cloning, Expression and Purification of human IL-17F, rat ILF, cynomolgus IL-17F and IL-17A

Cloning

The cDNAs encoding the mature human IL-17F (AF384857, aa 31-163) rat IL-17F (AAH91568, aa 21-153) cynomolgus IL-17F (identical to sequence XP_001106517 aa 31-163,) and cynomolgus IL-17A (identical to sequence XP_001106391, aa 20-155) were

amplified by PCR and cloned in PCR4TOPO vector (Invitrogen). Upon another PCR step, a His tag or a His tag followed by an AviTag (Avidity, Denver CO) were introduced at the N-terminus of the cytokine coding sequence. These constructs were then fused to a leader sequence and sub-cloned in a corresponding expression vectors.

Expression and purification of human IL-17F and rat IL-17F from baculovirus-infected cells

His-tagged huIL-17F or rat IL-17F preceded by the GP67 leader sequence (MLLVNQSHQGFNKEHTSKMVSAIVLYVLLAAAAHSAFA; SEQ ID NO:114) were sub-cloned into a baculovirus bacmid vector pFASTBAC Dual (Invitrogen). After transfection into Sf9 cells, recombinant virus was isolated and amplified. For protein production, Hi5 cells or SF9 cells were infected with baculovirus and incubated at 27°C for 3 days. Cell culture medium was cleared by centrifugation, filtered and concentrated about 10 times in SartoFlow Slice 200 (Sartorius - Hydrosart cutoff 10 kD). After adjustment of pH to 7.0 and another centrifugation step, the concentrated protein was purified using standard procedures on Ni-NTA Superflow columns (Qiagen) or HiTrap Chelating HP columns (GE Healthcare) charged with Ni^{2+} ions. IL-17F containing fractions were pooled and desalted on PD-10 columns (GE Healthcare).

Human IL-17F and rat IL-17F from baculovirus-infected cells were essentially free of contaminants after one purification step, and appeared predominantly as disulfide-linked homodimers as demonstrated by non-reducing SDS-PAGE. The biological activity of the His-tagged, baculovirus-expressed human IL-17F was comparable to the activity of commercial cytokines (*E.Coli* expressed huIL-17F, Peprotech EC or R&D Systems).

Expression and purification of human IL-17F and rat IL-17F from CHOK1SV cells

huIL-17F or rat IL-17F coding sequences preceded by the CD33 leader sequence (MPLLLLLPLLWAGALAMD; SEQ ID NO:115), plus a His tag, and an AviTag (Avidity, Denver CO) were placed under the control of the hCMV promoter in the expression vector pEE14.4. IL-17F was expressed from a bicistronic mRNA containing a viral internal ribosome entry site (IRES) and the GFP coding sequence as the second cistron. The pEE14.4.vector contains the glutamine synthetase (GS) gene, essential for the survival of transfected cells in selection medium containing methionine sulphoximine (MSX). Stable transfectants were generated in the CHOK1SV cell line, property of Lonza Biologics. After

four weeks of culture in the presence of MSX high-expressing clones were identified, expanded and used for the production of human or rat IL-17F.

CHOK1SV – expressed human IL-17F and rat IL-17F were purified by Ni^{2+} affinity chromatography. They were essentially free of contaminants and appeared as disulfide-linked homodimers on non-reducing SDS-PAGE gels. The biological activity of the His+Avi-tagged, CHO-expressed human IL-17F was significantly decreased as compared to the activity of the commercial huIL-17F, probably due to the presence of a bulky, double tag at the N-terminus.

Expression and purification of human IL-17F cnIL-17F and cnIL-17A from PEAK cells

His-tagged huIL-17A/F, cnIL-17F, or cnIL-17A coding sequences were fused to the *Gaussia princeps* luciferase leader sequence (AF015993) and placed under the control of the EF1 promoter in the episomal expression vector pEAK8. The cytokine-coding sequence was followed by a viral internal ribosome entry site (IRES) and a second cistron (GFP). The pEAK8 vector contains the puromycin resistance gene, the EBV nuclear antigen 1 (EBNA1) and the *oriP* origin of replication. EBNA1 and *oriP* are necessary for the propagation of the pEAK8 vector as episomal DNA in human cells and the generation of stable transfectants. Stably transfected cells were obtained after 7-10 days of culture in the presence of 2 ug/mL of puromycine. The populations of puromycine resistant cells were expanded and used for cytokine production.

PEAK – expressed purified by Ni^{2+} affinity chromatography were >95% pure and were found predominantly in the form of disulfide-linked homodimers, as demonstrated by non-reducing SDS-PAGE. The biological activity of the His-tagged, PEAK-expressed human IL-17F was similar to the activity of the huIL-17A/F from commercial sources.

EXAMPLE 2: Immunizations

Fully human monoclonal antibodies were generated using transgenic strains of mice in which mouse antibody gene expression was suppressed and replaced with human antibody gene expression. Three strains of transgenic mice were used:

1) HuMab® mouse (Medarex, Princeton NJ)
2) KM™ mouse, a crossbred between HuMAb Mouse and Kirin's TC Mouse (Kirin Pharma Company, Japan)

3) KM (FCγRIIb-KO) mouse, a strain derived from KM™ mouse, in which the gene *Fcgr2b* coding for the inhibitory Fc gamma Receptor IIB has been inactivated.

Mice were immunized either with human IL-17F or both human IL-17F and rat IL-17F. Two forms of antigen were used for immunizations: non-conjugated IL-17F or IL-17F conjugated to Keyhole Limpet Hemocyanin (KLH). Immunization strategies followed standard protocols from the literature.

Sera of immunized animals were screened periodically by ELISA for the presence of human IgG directed against huIL-17F, rat IL-17F, and huIL-17A (Peprotech EC cat No 200-17). Most of the animals developed high-titer responses to human IL-17F. When both rat IL-17F and huIL-17F were used for immunizations, most of the animals developed high-titer responses to both antigens. Importantly, a significant proportion of KM mice and KM (FCγRIIb-KO) mice immunized with both huIL-17F and rat IL-17F developed cross-reactive responses to huIL-17A. Cross-reactive responses were sporadically observed in KM and KM (FCγRIIb-KO) mice immunized with huIL-17F as the only antigen (*i.e.*, without rat IL-17F). Contrary to the KM and KM (FCγRIIb-KO) mice, HuMAb mice did not develop cross-reactive titers to huIL-17A, irrespective of the immunization protocol employed.

EXAMPLE 3: Generation of hybridomas

Fusion of Lymph Node Cells With SP2/0 Myeloma Cells

To obtain hybridomas, popliteal, inguinal, para-aortic, submandibular, cervical, axial, and brachial lymph nodes were removed from the mice and digested with collagenase and DNAse. Single cells suspension of lymph node cells was mixed at 1:1 ratio with SP2/0 myeloma cells and suspended in Cytofusion Low Conductivity Medium (CPS-LCMC, CytoPulse Sciences, Inc.). Fusions were done with 30 to 60 million splenocytes in the CytoPulse CEEF50 Electrofusion apparatus as indicated by the manufacturer (Cyto Pulse Sciences, Inc). After electrofusion, cells were incubated for approximately 1 hour at 37°C to allow recovery before distributing into 96-well plates.

Culture of Hybridomas

Fused cells were resuspended in HAT selection medium and plated in 44 to 52 96-well plates at a cell concentration of $0.1\text{-}0.2\times10^{5}$ splenocytes per well in 200 µl medium. Hybridoma selection proceeded for 14 days. Fusion of lymph nodes of immunized mice

resulted in the generation of hybridomas producing antibodies specific to huIL-17F or cross-reactive antibodies specific to both huIL-17F and huIL-17A.

Hybridoma Screening

Fourteen days after the fusion, hybridoma-containing plates were screened for the presence of human IgG binding to human IL-17F and/or human IL-17A by FLISA (Fluorescence- Linked Immunosorbent Assay). In brief, 6 micron beads (Polybeads, cat. No 07312, Polysciences Inc.) were coated with huIL-17F, huIL-17A (both from Peprotech EC) or BSA (Sigma) and were distributed into FMAT® 384-well optical plates (Applied Biosystems) at a density of 5,000 beads per well. The beads were mixed with a small volume of hybridoma culture supernatants (30 µl per well) and incubated overnight before addition of goat anti-human IgG Fc (Jackson Immunoresearch No 109-005-098) conjugated to FMAT Blue® dye (Applied Biosystems). After an incubation period of 2 to 8 hours the fluorescence of the beads was measured in an 8200 Cellular Detection System analyzer (Applied Biosystems). Hybridomas producing human IgGs that bound to huIL-17F, huIL-17A or both huIL-17F and huIL-17A, but not to BSA, were expanded and subjected to further analysis.

EXAMPLE 4: Cross-Reactivity of huIL-17F Antibodies

Binding assay: huIL-17F antibodies were tested for their ability to bind to the other members of the IL-17 family of cytokines, as well as to IL-17A and IL-17F from other species. The assay was performed in the FLISA format, as described above. The following recombinant cytokines were bound to polystyrene beads and tested for their ability to bind huIL-17F antibodies: hu IL17A-F heterodimer (R&D Systems, cat No 5194-IL-025/CF) (huIL17B (PeprotechEC, cat No 200-28), huIL-17C (R&D Systems, cat No 1234-IL-025/CF), huIL-17D (PeprotechEC, cat No 200-27), huIL-17E (huIL-25, PeprotechEC, cat No 200-24), muIL-17A (PeprotechEC, cat No 210-17), muIL-17F (PeprotechEC, cat No 200-17F), mu IL-17A-F heterodimer (R&D Systems, cat No 5390-IL-025/CF) rat IL-17F (His-tagged, produced in house in insect cells), rat IL-17A (His-tagged, produced in house in PEAK cells), cyIL-17F, cyIL-17A and the cyIL-17A-F heterodimer (all three produced in house in PEAK cells). The ability of the individual the huIL-17F antibodies to bind these different cytokines is summarized in Table 3 below:

Table 3: Cross-reactivity of huIL-17F antibodies as determined by FLISA

species	human							cynomolgus			mouse			rat	
dimer:	IL-17F	IL-17A	IL-17A/F	IL-17B	IL-17C	IL-17D	IL-17E	IL-17F	IL-17A	IL-17A/F	IL-17F	IL-17A	IL-17A/F	IL-17F	IL-17A
clone name															
30D12	+	+	+	-	-	-	-	+	+	+	-	-	-	+	+
29D8	+	+	+	-	-	-	-	+	+	+	-	-	-	-	-
1E4	+	+	+	-	-	-	-	+	+	+	-	-	-	-	-
31A3	+	+	+	-	-	-	-	+	+	+	-	-	-	-	-
5E12	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-
39F12	+	+	+	-	-	-	-	+	+	+	+	+	+	+	+
12B12	+	+	+	-	-	-	-	+	+	+	+	+	+	+	+
15B7	+	+	+	-	-	-	-	+	+	+	+	+	+	+	+
4H11	+	+	+	-	-	-	-	+	+	+	-	-	-	+	-
41B10	+	-	+	-	-	-	-	+	-	+	-	-	-	-	-
8B11	+	+	+	-	-	-	-	+	+	+	-	-	-	+	-
38B1	+	+	+	-	-	-	-	+	+	+	-	-	-	-	-
15E6	+	+	+	-	-	-	-	+	+	+	+	-	+	+	-
4B11	+	+	+	-	-	-	-	+	+	+	-	-	-	-	-

EXAMPLE 5: Measurement of affinity and binding kinetics of huIL-17A/F cross-reactive antibodies via Surface Plasmon Resonance (Biacore)

The affinity and binding kinetics of huIL-17F cross-reactive antibodies were characterized on a Biacore 2000 instrument (Biacore AB, Uppsala, Sweden). Three CM5 Biacore chips were used successively and 3600, 1800 and 1540 RU (response units) of an anti-human IgG Fc (Biacore AB, Uppsala, Sweden) were immobilized by EDC/NHS chemistry on these chips. This surface was used to capture huIL-17A/F antibodies. The surface was regenerated after each cycle by injection of 10mM glycine pH=1.5 at 20μL/min, for 30s followed by 1min of stabilization time in HBS-EP buffer (Biacore AB, Uppsala, Sweden).

Binding was measured by passing various IL-17 dimeric cytokines in duplicates at the following concentrations: 90nM, 30nM, 10nM, 3.33nM, 1.11nM and 0nM. All solutions were diluted in HBS-EP buffer. Injection was performed at 75μl/min for 3 min followed by 12min of dissociation time and the temperature was set at 25°C. Background subtraction binding curves were fitted according to 1:1 Langmuir model and the on-rate (k_a) off-rate (k_d) and dissociation constant (K_D) values determined. Tables 4 and 5 summarize the affinities and kinetic constants of huIL-17F cross-reactive antibodies.

Table 4: Affinity of huIL-17F cross-reactive antibodies for human IL-17 dimers

MAb	cytokine dimer	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_d (M)	K_d (pM)
15E6	huIL-17A	5.99 e+06	2.18 e-04	3.64 e-11	36.4
	huIL-17F	7.94 e+06	6.76 e-05	8.51 e-12	8.51
	huIL-17A/F	1.41 e+06	6.31 e-05	4.47 e-11	44.7
30D12	huIL-17A	1.71 e+06	1.02 e-04	5.94 e-11	59.4
	huIL-17F	2.31 e+06	6.61 e-04	2.86 e-10	286
	huIL-17A/F	1.02 e+06	1.00 e-04	9.81 e-11	98.1
39F12	huIL-17A	3.73 e+06	3.34 e-04	8.95 e-11	89.5
	huIL-17F	2.40 e+05	4.37 e-09	<1.00 e-12	<1.00
	huIL-17A/F	8.11 e+05	3.26 e-04	4.02 e-10	402

Table 5: Affinity of 15E6FK antibody for IL-17 dimers from different species

species	cytokine dimer	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_d (M)	K_d (pM)
human	IL-17A	1.91 e+06	2.24 e-05	1.17 e-11	11.7
	IL-17F	1.62 e+06	1.33 e-05	8.20 e-12	8.20
	IL-17A/F	5.50 e+05	1.34 e-05	2.44 e-11	24.4
cynomolgus	IL-17A	2.59 e+06	2.71 e-05	1.04 e-11	10.4
	IL-17F	2.39 e+06	8.25 e-06	3.45 e-12	3.45
	IL-17A/F	2.75 e+05	1.08 e-05	3.94 e-11	39.4
mouse	IL-17A	(-)	(-)	(-)	(-)
	IL-17F	2.30 e+06	5.55 e-04	2.36 e-10	236
	IL-17A/F	2.97 e+05	1.55 e-04	5.24 e-10	524
rat	IL-17A	(-)	(-)	(-)	(-)
	IL-17F	1.65 e+06	8.09 e-04	4.90 e-10	490

(-) no detectable binding

EXAMPLE 6: MAb 15E6FK/IL- 17 Receptor Binding Competition Studies

This study was performed to assess if the 15E6FK cross-reactive antibody competes with the IL- 17RA receptor for binding to IL- 17A.

Biacore competition binding studies were performed using immobilized 15E6FK antibody, soluble human IL-17A homodimers, and soluble recombinant human or mouse IL-17RA/Fc chimeras as competitors. An anti-human IgG-κ antibody was immobilized on a CM5 Biacore chip using EDC/NHS chemistry. This surface was used to capture the 15E6FK antibody. For competition studies, human IL-17A homodimer (30nM) was pre-incubated with excess of recombinant human or mouse IL17RA/Fc-fusion proteins (R&D Systems cat## 177-IR and 4481-MR) for 1 hour. Binding of various IL-17A-IL-17RA mixes was then measured on a Biacore 2000 instrument as described above (example 5). Pre-incubation of IL-17A with soluble receptor-IgG-Fc fusion proteins of human or mouse origin at 1:1 IL-17A to IL-17RA-Fc molar ratio reduced the binding of IL-17A to immobilized 15E6FK antibody by more than 90%. Pre-incubation of IL-17A with soluble receptor-IgG-Fc fusion proteins of human or mouse origin at 1:25 IL-17A to IL-17RA-Fc molar ratio eliminated this binding the binding of IL-17A to immobilized 15E6FK antibody altogether (~100% inhibition), demonstrating that the interactions of human IL-17A homodimers with IL-17RA receptors and the 15E6FK antibody are mutually exclusive.

EXAMPLE 7: Biological assays for IL-17F and IL-17A activity

IL-6 secretion by IL-17-stimulated Mouse Embryonic Fibroblasts

Human IL-17A and IL-17F bind the corresponding mouse IL-17 receptor. As a consequence, mouse fibroblasts can respond to both human IL-17A and IL-17F. Mouse C57BL/6 embryonic fibroblasts (MEF, ATCC No SCRC-1008) were therefore used to assay for huIL-17A and huIL-17F activity.

Briefly, MEF cells seeded in 96-well plates in DMEM + Glutamine + 10% Fetal Bovine Serum (FBS) were cultured for 48 h before the addition of cytokines, huIL-17A or huIL-17F and mouse TNFα at 10 ng/ml (Peprotech EC, cat No 315-01A). Co-stimulation with TNF was shown to synergize with IL-17 signaling (Ruddy et al. 2004, J.Biol.Chem 279:2559), significantly increasing the sensitivity of the mouse fibroblasts to IL-17A and IL-17F. In assays for MAb neutralizing activity, the IL-17 cytokines were pre-incubated with the antibody for 1 hour before adding to the cells. After 24 hours of stimulation in the presence of cytokines, supernatants were collected and the concentration of mouse IL-6 was measured by sandwich ELISA using rat anti mouse IL6 antibody (BD cat No 554400) for capture and a second, biotinylated, rat anti mouse IL6 antibody (BD 554402.) plus streptavidin HRP (Jackson Immunoresearch 016-030-084) for detection. Table 6 summarizes the IC_{50} values, obtained from IL-6 calibration curves using standard statistical techniques. Cynomolgus, mouse or rat IL-17A and IL-17F are also active in MEF cells and were tested against the monoclonal antibodies of the invention according to the methods described above.

Table 6: IC_{50} values for the inhibition of IL-17 cytokines from different species obtained with huIL-17F antibodies; n.t., not tested; (—) no inhibition was observed or IC_{50} could not be determined (IC_{50}>1 μM)

species	human			cynomolgus			mouse			rat	
IL-17 dimer:	IL-17F	IL-17A	IL-17A/F	IL-17F	IL-17A	IL-17A/F	IL-17F	IL-17A	IL-17A/F	IL-17F	IL-17A
IL-17 conc.	50 ng/ml	5 ng/ml	17.5 ng/ml	25 ng/ml	5 ng/ml	25 ng/ml	50 ng/ml	5 ng/ml	50 ng/ml	25 ng/ml	5 ng/ml
clone name	IC_{50} (nM)										
30D12	120	1.1	31	130	3.0	15	n.t.	n.t.	n.t.	27	(–)
30D12 BF	90	1.6	27	130	2.5	13	n.t.	n.t.	n.t.	30	(–)
29D8	1.5	40	1.1	3.6	8.4	0.56	n.t.	n.t.	n.t.	n.t.	n.t.
1E4	1.5	480	16	3.4	330	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
31A3	2.5	250	9.2	4.2	290	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
5E12	3.4	(–)	(–)	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
39F12	1.9	9.8	11	5.2	4.7	16	4.0	(–)	n.t.	n.t.	(–)
39F12A	1.3	13	4.4	n.t.	n.t.	n.t.	6.2	(–)	170	0.71	(–)
12B12	0.77	33	13	3.2	13	n.t.	4.2	(–)	n.t.	n.t.	(–)
15B7	6.4	180	160	15	140	n.t.	22	(–)	n.t.	n.t.	(–)
4H11	(–)	87	810	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
41B10	5.3	(–)	(–)	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
8B11	100	100	240	50	230	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
38B1	3.9	(–)	910	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.
15E6	1.7	1.6	1.1	1.4	2.0	0.18	(–)	n.t.	n.t.	(–)	n.t.
15E6FK	1.2	0.18	0.22	2.8	0.04	0.08	(–)	n.t.	(–)	(–)	n.t.
4B11	29	680	810	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.	n.t.

IL-6 secretion by IL-17-stimulated human fibroblasts

Human foreskin fibroblast (HFFF2, ECACC No 86031405) cells were seeded in 96-well plates in DMEM + Glutamine + 10% Foetal Bovine Serum (FBS) and cultured for 24 h before the addition of huIL-17A or cyIL-17A (25 ng/ml, 0.75 nM). In assays for MAb neutralizing activity, IL-17A was pre-incubated with the antibody for 1 hour before adding to the cells. After 24 hours of stimulation, supernatants were collected and the concentration of human IL-6 was measured by sandwich ELISA using an anti human IL6 antibody (Endogen cat No M620) for capture and a biotinylated anti human IL6 antibody (Endogen M621B) + streptavidin HRP (Jackson Immunoresearch 016-030-084) for detection. Table 7 summarizes IC_{50} values obtained from IL-6 calibration curves using standard statistical techniques.

Table 7: IC_{50} values for the inhibition of human and cynomolgus IL-17A homodimers obtained with cross-reactive huIL-17F antibodies; n.t., not tested; (—) no inhibition was observed or IC_{50} could not be determined (IC_{50}>1 μM)

species	human	cynomolgus
IL-17 dimer:	IL-17A	
IL-17 conc.	25 ng/ml	25 ng/ml
clone name	IC_{50} (nM)	
30D12	4.2	6.6
30D12 BF	3.0	5.7
29D8	36	n.t.
39F12	14	15
39F12A	21	20
4H11	108	n.t.
15E6	3.9	4.5
15E6FK	0.83	0.76
4B11	(–)	n.t.

EXAMPLE 8. Epitope characterization.

The 15E6FK antibody binds human IL-17A (Accession No. Q16552) and cynomolgus IL-17A (NCBI Accession No. XP_001106391) but not rat IL-17A (Accession No. Q61453) or mouse IL-17A (Accession No. Q62386). The 15E6FK antibody also binds human IL-17F(Accession No. Q96PD4), cynomolgus IL-17F(NCBI Accession No. XP_001106517), rat IL-17F (Accession No. Q5BJ95), and mouse IL-17F (Accession No. Q8K4C3).

Based on these observations, a targeted mutagenesis was performed in order to find amino acid residues critical for binding to human and cynomolgus cytokines. The mutagenesis was limited to residues that are common between human and cynomolgus IL-17A but are different in mouse and rat IL-17A.

For these experiments, specific residues in human IL-17A (21T, 27N, 28I, 32N, 52N, 70K, 74L, 75G, 91P, 100R, 108N, 109S, 126P, 125T, 126P, 129H, 130H, 131V, and 132A) or clusters of residues (LG, residues 74-75; NSFRL, residues 108 to 112 or PIVH, residues 126 to 129) were substituted with amino acids found at the corresponding position in the mouse IL-17A sequence, and the resulting mutant cytokines were expressed in mammalian cells as described in Example 1.

Binding of 15E6FK to mutant cytokines was determined by sandwich ELISA, using rabbit anti human IL-17A polyclonal antibody (R&D Systems, cat # 500-P07) for the capture of the cytokine and using 15E6FK with anti-human IgG kappa-HRP antibody for detection.. L74Q and G75R were the only two amino acid substitutions that affected 15E6 binding: L74Q reduced 15E6FK binding by more than 70%, while the G75R point mutation or the LG to QR double mutation totally abolished binding. None of the other single or multiple amino acid substitutions affected binding of 15E6FK to huIL-17A.

The importance of these two residues for 15E6FK binding was further confirmed by mutating the corresponding residues in human IL-17F (L75S and G76R) followed by a huIL-17F sandwich ELISA using rabbit anti human IL-17F polyclonal antibody for the capture (R&D Systems, cat # 500-P90). Similar as observed with huIL-17A:

1) L75S substitution in the human IL-17F sequence reduced 15E6FK binding,
2) G76R substitution abolished 15E6FK binding altogether
3) None of the other single or multiple amino acid mutations in huIL-17F (residues 92P, 109V, 110S, 126T, 127P, 131H, 126-131TPVIHH) affected binding of 15E6FK

In conclusion, residue G75 of human IL-17A (G76 in human IL-17F) is absolutely required for 15E6FK binding, and the adjacent residue L74 (L75 in human IL-17F) plays a minor role. These two residues thus form an essential part of the epitope recognized by mAb 15E6FK.

EXAMPLE 9 Binding interference experiments.

To assess if two different antibodies can bind simultaneously to huIL-17F or huIL-17A, a series of binding interference experiments were performed by FLISA (Fluorescence-Linked Immunosorbent Assay). For these experiments, four antibodies were tested for binding interference (binding competition): 15E6, 29D8, 30D12, and 39F12. These four antibodies were either labeled with fluorescent dye conjugate (FMAT Blue, Applied Biosystems) for binding detection, or were used non-labeled as competitors.

For these experiments, microbeads coated with huIL-17F or huIL-17A were distributed into FMAT® 384-well optical plates (Applied Biosystems) and were pre-incubated with increasing concentrations of non-labeled, competitor antibody for 24 hours (0.1 μg/ml to 60 μg/ml; i.e., 2- to 1200-fold excess over the detection antibody). After the pre-incubation with competitor, fluorescently labeled detection antibody was added to a final concentration of 50 ng/ml, and the incubation was continued. The fluorescence of the beads was measured at different time points (1 to 24 hours after addition of the detection antibody) using the 8200 Cellular Detection System Analyzer (Applied Biosystems).

Antibodies that recognize the same epitope or an overlapping epitope competed for binding and were not able to bind simultaneously to the antigen. In this case, high concentrations of competitor antibody resulted in total extinction of bead fluorescence. In contrast, antibodies that recognize non-overlapping, spatially separated epitopes did not interfere with each other and were able to bind simultaneously (competitor antibody did not affect bead fluorescence). Alternatively, partial binding interference could be observed as a consequence of steric hindrance between two antibodies binding in close proximity to two neighboring epitopes (competitor antibody decreased bead fluorescence but only partially, even at the highest concentrations). On the basis of these binding interference experiments, four antibodies were assigned to three families or "epitope bins":

1) 15E6 and 29D8
2) 30D12
3) 39F12

Binding of 15E6 or 29D8 (bin 1) partially interfered with binding of 30D12 (bin 2). In contrast, binding of 39F12 (bin 3) did not interfere with the binding of the other three antibodies (bins 1 and 2). Therefore, the epitope bound by 39F12 is spatially separated from the epitopes bound by 15E6, 29D8, or 30D12.

What is claimed is:

1. An isolated fully human monoclonal antibody that binds IL-17A homodimer, IL-17F homodimer and the IL-17A/IL-17F heterodimeric complex, wherein the antibody exhibits (i) a binding affinity of at least 100 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 300 pM or less against the IL-17F homodimer, (iii) a binding affinity of at least 400 pM or less against the IL-17A/IL-17F heterodimeric complex, (iv) a neutralizing ability of at least 13 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 120 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 31 nM or less against the IL-17A/IL-17F heterodimeric complex.

2. The antibody of claim 1, wherein the antibody exhibits (i) a binding affinity of at least 40 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 10 pM or less against the IL-17F homodimer, and (iii) a binding affinity of at least 50 pM or less against the IL-17A/IL-17F heterodimer.

3. The antibody of claim 1, wherein the antibody exhibits (i) a binding affinity of at least 15 pM or less against the IL-17A homodimer, (ii) a binding affinity of at least 10 pM or less against the IL-17F homodimer, and (iii) a binding affinity of at least 30 pM or less against the IL-17A/IL-17F heterodimer.

4. The antibody of claim 1, wherein the antibody exhibits, (iv) a neutralizing ability of at least 13 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.9 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 11 nM or less against the IL-17A/IL-17F heterodimeric complex.

5. The antibody of claim 1, wherein the antibody exhibits, (iv) a neutralizing ability of at least 1.6 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.7 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 1.1 nM or less against the IL-17A/IL-17F heterodimeric complex.

6. The antibody of claim 1, wherein the antibody exhibits, (iv) a neutralizing ability of at least 0.2 nM or less against the IL-17A homodimer, (v) a neutralizing ability of at least 1.2 nM or less against the IL-17F homodimer, and (vi) a neutralizing ability of at least 0.2 nM or less against the IL-17A/IL-17F heterodimeric complex.

7. The antibody of claim 1, wherein the antibody is 15E6 and comprises a VH CDR1 sequence comprising the amino acid sequence of SEQ ID NO: 85, a VH CDR2 sequence comprising the amino acid sequence of SEQ ID NO: 86, a VH CDR3 sequence comprising the amino acid sequence of SEQ ID NO: 87, a VL CDR1 sequence comprising the amino acid sequence of SEQ ID NO: 110, a VL CDR2 sequence comprising the amino acid sequence of SEQ ID NO: 97 and a VL CDR3 sequence comprising the amino acid sequence of SEQ ID NO: 111.

8. The antibody of claim 1, wherein the antibody is 15E6FK and comprises a VH CDR1 sequence comprising the amino acid sequence of SEQ ID NO: 85, a VH CDR2 sequence comprising the amino acid sequence of SEQ ID NO: 94, a VH CDR3 sequence comprising the amino acid sequence of SEQ ID NO: 95, a VL CDR1 sequence comprising the amino acid sequence of SEQ ID NO: 110, a VL CDR2 sequence comprising the amino acid sequence of SEQ ID NO: 97 and a VL CDR3 sequence comprising the amino acid sequence of SEQ ID NO: 111..

9. The antibody of claim 1, wherein the antibody binds to the same epitope as the 15E6 antibody.

10. The antibody of claim 1, wherein the antibody binds to the same epitope as the 15E6FK antibody.

11. The antibody of claim 1, wherein the antibody binds IL-17A, IL-17F and the IL-17A/IL-17F heterodimeric complex and prevents one or more of IL-17F, IL-17A or the IL-17A/IL-17F heterodimeric complex from binding with its receptor.

12. An isolated fully human monoclonal antibody, or fragment thereof, wherein said antibody comprises:

(a) a V_H CDR1 region comprising the amino acid sequence of SEQ ID NO: 57, 60, 66, 69, 76, 79, 82, or 85;

(b) a V_H CDR2 region comprising the amino acid sequence of SEQ ID NO: 58, 61, 63, 65, 67, 70, 72, 74, 77, 80, 83, 86, 93 or 94;

(c) a V_H CDR3 region comprising the amino acid sequence of SEQ ID NO: 59, 62, 64, 68, 71, 73, 75, 78, 81, 84, 87, or 95;

(d) a V_L CDR1 region comprising the amino acid sequence of SEQ ID NO: 96, 101, 104, 107 or 110;

(e) a V_L CDR2 region comprising the amino acid sequence of SEQ ID NO: 97, 102, 105 or 108; and

(f) a V_L CDR3 region comprising the amino acid sequence of SEQ ID NO: 98, 99, 100, 103, 106, 109, or 111,

wherein said antibody binds IL-17F and IL-17A.

13. The antibody of claim 12, wherein said antibody also binds the IL-17A/IL-17F heterodimeric complex.

14. The antibody of claim 12, wherein said antibody is an IgG isotype.

15. The antibody of claim 12, wherein said antibody is an IgG1 isotype.

16. The antibody of claim 12, wherein said antibody comprises a heavy chain variable sequence comprising an amino acid sequence selected from SEQ ID NO: 2, 6, 8, 10, 14, 18, 20, 24, 28, 32, 34, 38, 52, and 54.

17. The antibody of claim 12, wherein said antibody further comprises a light chain variable sequence comprising the amino acid sequence selected from SEQ ID NO: 4, 12, 16, 22, 26, 30, 36, 40 and 56.

18. An isolated fully human monoclonal antibody comprising a heavy chain variable sequence comprising the amino acid sequence of SEQ ID NO: 2, 6, 8, 10, 14, 18, 20, 24, 28, 32, 38, 52, or 54, and a light chain variable sequence comprising the amino acid sequence of

SEQ ID NO: 4, 12, 16, 22, 26, 30, 36, 40, or 56, wherein said antibody binds IL-17F and IL-17A.

19. The antibody of claim 18, wherein said antibody is an IgG isotype.

20. The antibody of claim 18, wherein said antibody is an IgG1 isotype.

21. An isolated fully human monoclonal antibody, or fragment thereof, wherein said antibody comprises:

(a) a V_H CDR1 region comprising the amino acid sequence of SEQ ID NO: 85 or 90;

(b) a V_H CDR2 region comprising the amino acid sequence of SEQ ID NO: 88 or 91;

(c) a V_H CDR3 region comprising the amino acid sequence of SEQ ID NO: 89 or 92;

(d) a V_L CDR1 region comprising the amino acid sequence of SEQ ID NO: 101 or 107;

(e) a V_L CDR2 region comprising the amino acid sequence of SEQ ID NO: 102 or 108; and

(f) a V_L CDR3 region comprising the amino acid sequence of SEQ ID NO: 112 or 113,

wherein said antibody binds IL-17F.

22. The antibody of claim 21, wherein said antibody does not bind IL-17A or IL-17A homodimer.

23. The antibody of claim 21, wherein said antibody is an IgG isotype.

24. The antibody of claim 21, wherein said antibody comprises a heavy chain variable sequence comprising an amino acid sequence selected from SEQ ID NO: 44 and 48.

25. The antibody of claim 21, wherein said antibody further comprises a light chain variable sequence comprising the amino acid sequence of SEQ ID NO: 46 and 50.

26. A pharmaceutical composition comprising an antibody of any one of the preceding claims and a carrier.

27. A method of alleviating a symptom of a clinical indication associated rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis chronic obstructive pulmonary disease, or asthma in a subject, the method comprising administering an antagonist of the IL-17A/IL-17F heterodimeric complex to a subject in need thereof in an amount sufficient to alleviate the symptom of the clinical indication associated with rheumatoid arthritis, Crohn's disease, psoriasis, multiple sclerosis chronic obstructive pulmonary disease, or asthma.

28. The method of claim 27, wherein said subject is a human.

29. The method of claim 27, wherein said antagonist is a monoclonal antibody or fragment thereof.

30. The method of claim 29, wherein said monoclonal antibody is an antibody according to any one of claims 1 to 20 or fragment thereof.

31. A method of alleviating a symptom of an autoimmune disease, inflammatory disorder or cell proliferation disorder, wherein the method comprises administering an antibody according to any one of claims 1 to 25 to a subject in need thereof in an amount sufficient to alleviate the symptom of the autoimmune disease, inflammatory disorder or cell proliferation disorder in the subject.

32. The method of claim 31, wherein said subject is a human.

SEQUENCE LISTING

<110> NovImmune SA
Masternak, Krzysztof
Leger, Olivier

<120> Anti-IL-17A/IL-17F Cross-Reactive Antibodies and Methods of Use Thereof

<130> 23135-415001WO

<140> IB2009/005796
<141> 2009-05-05

<150> US 61/126465
<151> 2008-05-05

<150> US 61/098369
<151> 2008-09-26

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20 25 30

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35 40 45

Gly Trp Met Asn Pro Asp Ser Gly Val Ile Arg Tyr Ala Gln Lys Phe
50 55 60

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65                  70                  75                  80

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

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

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            20                  25                  30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
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cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatagtaa cacaaactat 180

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20 25 30

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

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

Gln Gly Arg Ile Thr Met Thr Thr Asp Thr Ser Thr Arg Thr Ala Tyr
65 70 75 80

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

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

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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Ser Val Lys Val Ser Cys Lys Ala Ser Val Tyr Thr Phe Thr Thr Tyr
20 25 30

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

Gly Trp Ile Ser Val Tyr Asn Gly Asn Thr Asn Tyr Gly Gln Asn Phe
50 55 60

Gln Gly Arg Val Ser Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Ser Phe His Gly Gly His Ser Gly Tyr His Tyr Gly Leu Asp Val
100 105 110

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

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gcacagaagt tccacggcag agtcaccatg accacagaca catccacaag tacagcctac 240

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20 25 30

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

Gly Trp Ile Thr Val Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

His Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Ser Phe His Gly Gly His Ser Gly Tyr His Tyr Gly Leu Asp Val
100 105 110

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

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

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

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

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

Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
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cagcccccag ggaaggggct ggagtggatt gggagtatct attatagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagtcacc atatccgtag acacgtccaa gaaccagttc 240

tccctgaaag tgagttctgt gaccgccaca gacacggctg tgtattactg tgcgagagtc 300

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35 40 45

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

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

Ser Leu Lys Val Ser Ser Val Thr Ala Thr Asp Thr Ala Val Tyr Tyr
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Gln Gly Thr Leu Val Thr Val Ser Ser
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20 25 30

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

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

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

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

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<212> PRT
<213> Homo sapiens

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

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

Gly Gly Ile Ile Pro Phe Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Ile Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65 70 75 80

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

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atggagctga gcagcctgag atctgaggac acggccgtgt attactgtgc gagagacagg 300

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

Gly Gly Ile Ile Pro Phe Phe Gly Thr Val Asn Tyr Ala Gln Lys Phe
50 55 60

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Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80

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

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

Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
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aggttcagtg gcagtggatc tgggacagat ttcaccctca ccatcaatag cctggaagct 240

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<400> 22

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Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
            20                  25                  30

Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Ala Ala Ala Tyr Tyr Cys His Gln Ser Ser Ser Leu Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
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tccgggaaag ggctggactg ggttggccgt attagaagca aagctaacag ttacgcgaca 180

gcatatgctg cgtcggtgat aggcaggttc accatctcca gagatgattc aaagaacacg 240

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<400> 24

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

Ser Met His Trp Val Arg Gln Ala Ser Gly Lys Gly Leu Asp Trp Val
35 40 45

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

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

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

Tyr Cys Thr Thr Ser Val Ala Thr Thr Leu Thr Asp Tyr Tyr Gly Met
100 105 110

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

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<212> DNA
<213> Homo sapiens

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ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

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gaagattttg cagtttatta ctgtcaacag cgtagcaact ggcctccatt cactttcggc 300

cctgggacca aagtggatat caaa 324

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<400> 26

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1 5 10 15

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

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

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

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

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

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

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<211> 357
<212> DNA
<213> Homo sapiens

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gcagactctg tgaagggccg attcaccatc tccagagaca atgccaggaa ctcactgtat 240

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tactatggcc acggatttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

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<211> 119
<212> PRT
<213> Homo sapiens

<400> 28

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20 25 30

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

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

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

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

Ala Arg Val Ser Tyr Tyr Gly His Gly Phe Asp Tyr Trp Gly Gln Gly
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Thr Leu Val Thr Val Ser Ser
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gagaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgccaacag tataatagtt accctctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

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<400> 30

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

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

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

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

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

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

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cctggacaag ggcttgagtg gatgggagga atcatccctt tctttggaac agcacactac 180

gcacagaagt tccagggcag agtcacgatt accgcggacg aatccacgaa cacagcctac 240

atggagctga gcagcctgag atctgaggac acggccgtat attactgtgc gagagatagg 300

gactactatg gttcggggag tcccttccac ttctccggtt tggacgtctg gggccaaggg 360

accacggtca ccgtctcctc a 381

<210> 32
<211> 127
<212> PRT
<213> Homo sapiens

<400> 32

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

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

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

Gly Gly Ile Ile Pro Phe Phe Gly Thr Ala His Tyr Ala Gln Lys Phe
50 55 60

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Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80

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

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

Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
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<210> 33
<211> 369
<212> DNA
<213> Homo sapiens

<400> 33
gaagtacagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttgat gattttgcca tgcactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt attaattgga atagtggtag cataggctat 180

gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agccgaggac acggccttgt attactgtgc aaaagatata 300

gcagcagctg gtgaattcta cttcgatatg gacgtctggg gccaagggac cacggtcacc 360

gtctcctca 369

<210> 34
<211> 123
<212> PRT
<213> Homo sapiens

<400> 34

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

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

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

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

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

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95
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Ala Lys Asp Ile Ala Ala Ala Gly Glu Phe Tyr Phe Asp Met Asp Val
100 105 110

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

<210> 35
<211> 321
<212> DNA
<213> Homo sapiens

<400> 35
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcctccgac ttttggccag 300

gggaccaagc tggagatcaa a 321

<210> 36
<211> 107
<212> PRT
<213> Homo sapiens

<400> 36

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

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

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

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

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

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

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

<210> 37
<211> 369
<212> DNA
<213> Homo sapiens

<400> 37

gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt attaattgga atagtggtgg cataggctat 180

gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aagagatatg 300

gggggttcg gggagtttta ctggaacttc ggtctctggg gccgtggcac cctggtcact 360

gtctcctca 369

<210> 38
<211> 123
<212> PRT
<213> Homo sapiens

<400> 38

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

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

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

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

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

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

Ala Arg Asp Met Gly Gly Phe Gly Glu Phe Tyr Trp Asn Phe Gly Leu
100 105 110

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 39
<211> 324
<212> DNA
<213> Homo sapiens

<400> 39
gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttaga agctacttag cctggtacca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcctccggc cactttcggc 300

ggagggacca aggtggagat caaa 324

<210> 40
<211> 108
<212> PRT
<213> Homo sapiens

<400> 40

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

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

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

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

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

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

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

<210> 41
<400> 41
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<210> 42
<400> 42
000

<210> 43
<211> 375
<212> DNA
<213> Homo sapiens

<400> 43
caggtgcagc tggtgcagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtac cataggctat 180

gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aaaagaactg 300

tatatcagtg actgggactc ctactcctac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> 44
<211> 125
<212> PRT
<213> Homo sapiens

<400> 44

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

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

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

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

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

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

Ala Lys Glu Leu Tyr Ile Ser Asp Trp Asp Ser Tyr Ser Tyr Gly Met
100 105 110

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

<210> 45
<211> 318
<212> DNA
<213> Homo sapiens

<400> 45
gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttagc agcagctact tagcctggta ccagcagaaa 120

cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180

gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240

cctgaagatt ttgcagtgta ttactgtcag cagtatggta gctcaccttt cggcggaggg 300

accaaggtgg agatcaaa 318

<210> 46
<211> 106
<212> PRT
<213> Homo sapiens

<400> 46

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

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

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

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

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

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

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

<210> 47
<211> 372
<212> DNA
<213> Homo sapiens

<400> 47
gaggtgcagc tggtggagtc tgggggaggc ttggtaaagc ctgggggtc ccttagactc 60

tcctgtgcag cctctggatt cactttcagt aacgcctgga tgagctgggt ccgccaggct 120

ccagggaagg ggctggaatg ggttggccgt attaaaagca aaactgatgg tgggacaaca 180

gactacgttg cacccgtgaa aggcagattc accatctcaa gagatgattc aaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaggacacag ccgtatatta ctgtaccaca 300

tcgtatagca gttactggtt cccctactac tttgactact ggggccaggg aaccctggtc 360

accgtctcct ca 372

<210> 48
<211> 124
<212> PRT
<213> Homo sapiens

<400> 48

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

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

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

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

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

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

Tyr Cys Thr Thr Ser Tyr Ser Ser Tyr Trp Phe Pro Tyr Tyr Phe Asp
100 105 110

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

<210> 49
<211> 321
<212> DNA
<213> Homo sapiens

<400> 49
gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120

gagaaagccc ctaagtccct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgccaacag tataatagtt acccgatcac cttcggccaa 300

gggacacgac tggagattaa a 321

<210> 50
<211> 107
<212> PRT
<213> Homo sapiens

<400> 50

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

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

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

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

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

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

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

<400> 51
caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccttcacc agttatgata tcaactgggt gcgacaggcc 120

actggacaag ggcttgagtg gatgggatgg ctgaaccctg acagtggtgt catacgttat 180

gcacagaagt tccagggtag agtcaccatg accagggaca cctccataag cacagcctac 240

atggagctaa gcagcctgag atctgaggac acggccgtgt attactgtgc gagagaatgg 300

ttcggggagt taccctctta ctacttctac tccggtatgg acgtctgggg ccaagggacc 360

acggtcaccg tctcctca 378

<210> 52
<211> 126
<212> PRT
<213> Homo sapiens

<400> 52

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

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

Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Leu Asn Pro Asp Ser Gly Val Ile Arg Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

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

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

<210> 53
<211> 369
<212> DNA
<213> Homo sapiens

<400> 53
gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt attaattgga gcagtggtgg cataggctat 180

gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag agctgaggac acggccttgt attactgtgc aagagatatc 300

gggggttcg gggagtttta ctggaacttc ggtctctggg gccgtggcac cctggtcact 360

gtctcctca 369

<210> 54
<211> 123
<212> PRT
<213> Homo sapiens

<400> 54

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

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

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

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

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

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

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

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 55
<211> 321
<212> DNA
<213> Homo sapiens

<400> 55
gaaattgtgt tgacacagtc tccagacttt cagtctgtga ctccaaagga gaaagtcacc 60

atcacctgcc gggccagtca gagcattggt agtagcttac actggtacca gcagaaacca 120

gatcagtctc caaagctcct catcaagtat gcttcccagt ccttctcagg ggtcccctcg 180

aggttcagtg gcagtggatc tgggacagat ttcaccctca ccatcaatag cctggaagct 240

gaagatgctg caacgtatta ctgtcatcag agtagtagtt taccgtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> 56
<211> 107
<212> PRT
<213> Homo sapiens

<400> 56

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
20 25 30

Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
35 40 45

Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Ser Ser Ser Leu Pro Trp
85 90 95

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

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

<400> 57

Ser Tyr Asp Ile Asn
1 5

<210> 58
<211> 17
<212> PRT
<213> Homo sapiens

<400> 58

Trp Met Asn Pro Asp Ser Gly Val Ile Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 59
<211> 17
<212> PRT
<213> Homo sapiens

<400> 59

Glu Trp Phe Gly Glu Leu Pro Ser Tyr Tyr Phe Tyr Ser Gly Met Asp
1 5 10 15

Val

<210> 60
<211> 5
<212> PRT
<213> Homo sapiens

<400> 60

Thr Tyr Gly Ile Ser
1 5

<210> 61
<211> 17
<212> PRT
<213> Homo sapiens

<400> 61

Trp Ile Ser Ala Tyr Asn Ser Asn Thr Asn Tyr Ala Gln Lys Val Gln
1 5 10 15

Gly

<210> 62
<211> 14
<212> PRT
<213> Homo sapiens

<400> 62

Phe Phe Gly Gly His Ser Gly Tyr His Tyr Gly Leu Asp Val
1 5 10

<210> 63
<211> 17
<212> PRT
<213> Homo sapiens

<400> 63

Trp Ile Ser Val Tyr Asn Gly Asn Thr Asn Tyr Gly Gln Asn Phe Gln
1 5 10 15

Gly

<210> 64

<211> 14
<212> PRT
<213> Homo sapiens

<400> 64

Phe His Gly Gly His Ser Gly Tyr His Tyr Gly Leu Asp Val
1 5 10

<210> 65
<211> 17
<212> PRT
<213> Homo sapiens

<400> 65

Trp Ile Thr Val Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Phe His
1 5 10 15

Gly

<210> 66
<211> 7
<212> PRT
<213> Homo sapiens

<400> 66

Ser Arg Ser Tyr Tyr Trp Gly
1 5

<210> 67
<211> 16
<212> PRT
<213> Homo sapiens

<400> 67

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

<210> 68
<211> 11
<212> PRT
<213> Homo sapiens

<400> 68

Val Ser Gly Trp Asn Gly Asn Trp Phe Asp Pro
1 5 10

<210> 69
<211> 5
<212> PRT
<213> Homo sapiens

<400> 69

Ser Tyr Ala Phe Ser
1 5

<210> 70
<211> 17
<212> PRT
<213> Homo sapiens

<400> 70

Gly Ile Ile Pro Phe Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 71
<211> 18
<212> PRT
<213> Homo sapiens

<400> 71

Asp Arg Asp Tyr Tyr Gly Leu Gly Ser Pro Phe Tyr Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> 72
<211> 17
<212> PRT
<213> Homo sapiens

<400> 72

Gly Ile Ile Pro Phe Phe Gly Thr Val Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 73
<211> 18
<212> PRT
<213> Homo sapiens

<400> 73

Asp Arg Asp Tyr Tyr Gly Leu Gly Ser Pro Leu His Tyr Tyr Gly Leu
1 5 10 15

Asp Val

<210> 74
<211> 17
<212> PRT
<213> Homo sapiens

<400> 74

Gly Ile Ile Pro Phe Phe Gly Thr Ala His Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 75
<211> 18
<212> PRT
<213> Homo sapiens

<400> 75

Asp Arg Asp Tyr Tyr Gly Ser Gly Ser Pro Phe His Phe Ser Gly Leu
1 5 10 15

Asp Val

<210> 76
<211> 5
<212> PRT
<213> Homo sapiens

<400> 76

Gly Ser Ser Met His
1 5

<210> 77
<211> 19
<212> PRT
<213> Homo sapiens

<400> 77

Arg Ile Arg Ser Lys Ala Asn Ser Tyr Ala Thr Ala Tyr Ala Ala Ser
1 5 10 15

Val Ile Gly

<210> 78
<211> 14
<212> PRT
<213> Homo sapiens

<400> 78

Ser Val Ala Thr Thr Leu Thr Asp Tyr Tyr Gly Met Asp Val
1 5 10

<210> 79
<211> 5
<212> PRT
<213> Homo sapiens

<400> 79

Ser Phe Asn Met Asp

1 5

<210> 80
<211> 17
<212> PRT
<213> Homo sapiens

<400> 80

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

Gly

<210> 81
<211> 10
<212> PRT
<213> Homo sapiens

<400> 81

Val Ser Tyr Tyr Gly His Gly Phe Asp Tyr
1 5 10

<210> 82
<211> 5
<212> PRT
<213> Homo sapiens

<400> 82

Asp Phe Ala Met His
1 5

<210> 83
<211> 17
<212> PRT
<213> Homo sapiens

<400> 83

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

Gly

<210> 84
<211> 14
<212> PRT
<213> Homo sapiens

<400> 84

Asp Ile Ala Ala Ala Gly Glu Phe Tyr Phe Asp Met Asp Val
1 5 10

<210> 85
<211> 5

<212> PRT
<213> Homo sapiens

<400> 85

Asp Tyr Ala Met His
1 5

<210> 86
<211> 17
<212> PRT
<213> Homo sapiens

<400> 86

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

Gly

<210> 87
<211> 14
<212> PRT
<213> Homo sapiens

<400> 87

Asp Met Gly Gly Phe Gly Glu Phe Tyr Trp Asn Phe Gly Leu
1 5 10

<210> 88
<211> 17
<212> PRT
<213> Homo sapiens

<400> 88

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

Gly

<210> 89
<211> 16
<212> PRT
<213> Homo sapiens

<400> 89

Glu Leu Tyr Ile Ser Asp Trp Asp Ser Tyr Ser Tyr Gly Met Asp Val
1 5 10 15

<210> 90
<211> 5
<212> PRT
<213> Homo sapiens

<400> 90

Asn Ala Trp Met Ser
1 5

<210> 91
<211> 19
<212> PRT
<213> Homo sapiens

<400> 91

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

Val Lys Gly

<210> 92
<211> 13
<212> PRT
<213> Homo sapiens

<400> 92

Ser Tyr Ser Ser Tyr Trp Phe Pro Tyr Tyr Phe Asp Tyr
1 5 10

<210> 93
<211> 17
<212> PRT
<213> Homo sapiens

<400> 93

Trp Leu Asn Pro Asp Ser Gly Val Ile Arg Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 94
<211> 17
<212> PRT
<213> Homo sapiens

<400> 94

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

Gly

<210> 95
<211> 14
<212> PRT
<213> Homo sapiens

<400> 95

Asp Ile Gly Gly Phe Gly Glu Phe Tyr Trp Asn Phe Gly Leu

1 5 10

<210> 96
<211> 11
<212> PRT
<213> Homo sapiens

<400> 96

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

<210> 97
<211> 7
<212> PRT
<213> Homo sapiens

<400> 97

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 98
<211> 9
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<213> Homo sapiens

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Ser Lys Met Val Ser Ala Ile Val Leu Tyr Val Leu Leu Ala Ala Ala
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Ala His Ser Ala Phe Ala
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Ala Met Asp