TREATMENT OF INSULIN-RESISTANT DISORDERS

FIELD OF THE INVENTION

The invention concerns the treatment of insulin-resistant disorders. In particular, the invention concerns the treatment of insulin-resistant disorders by administration of IL-17, such as IL-17A and/or IL-17F antagonists, such as anti-IL-17A and/or IL-17F and/or IL-17Rc antibodies, or antibody fragments.

BACKGROUND OF THE INVENTION

The IL-17 family

Interleukin-17A (IL-17A) is a T-cell derived pro-inflammatory molecule that stimulates epithelial, endothelial and fibroblastic cells to produce other inflammatory cytokines and chemokines including IL-6, IL-8, G-CSF, and MCP-1 (see, Yao, Z. et al., J. Immunol., 122(12):5483-5486 (1995); Yao, Z. et al, Immunity, 3(6):811-821 (1995); Fossiez, F., et al., J. Exp. Med., 183(6): 2593-2603 (1996); Kennedy, J., et al., J. Interferon Cytokine Res., 16(8):611-7 (1996); Cai, X. Y., et al., Immunol. Lett, 62(1):51-8 (1998); Jovanovic, D.V., et al., J. Immunol., 160(7):3513-21 (1998); Laan, M., et al., J. Immunol., 162(4):2347-52 (1999); Linden, A., et al., Eur Respir J, 15(5):973-7 (2000); and Aggarwal, S. and Gurney, A. L., J Leukoc Biol. 71(1):1-8 (2002)). IL-17 also synergizes with other cytokines including TNF-α and IL-1β to further induce chemokine expression (Chabaud, M., et al., J. Immunol. 161(1):409-14 (1998)). IL-17A exhibits pleitropic biological activities on various types of cells. IL-17A also has the ability to induce ICAM-1 surface expression, proliferation of T cells, and growth and differentiation of $CD34^+$ human progenitors into neutrophils. IL-17A has also been implicated in bone metabolism, and has been suggested to play an important role in pathological conditions characterized by the presence of activated T cells and TNF-α production such as rheumatoid arthritis and loosening of bone implants (Van Bezooijen et al., J. Bone Miner. Res., 14: 1513-1521 (1999]). Activated T cells of synovial tissue derived from rheumatoid arthritis patients were found to secrete higher amounts of IL-17A than those derived from normal individuals or osteoarthritis patients (Chabaud et al., Arthritis Rheum., 42: 963-970 (1999)). It was suggested that this proinflammatory cytokine actively contributes to synovial inflammation in rheumatoid arthritis. Apart from its proinflammatory role, IL-17A seems to contribute to the pathology of rheumatoid arthritis by yet another mechanism. For example, IL-17A has been

shown to induce the expression of osteoclast differentiation factor (ODF) mRNA in osteoblasts (Kotake et al., J. Clin. Invest., 103: 1345-1352 (1999)). ODF stimulates differentiation of progenitor cells into osteoclasts, the cells involved in bone resorption. Since the level of IL-17A is significantly increased in synovial fluid of rheumatoid arthritis patients, it appears that IL-17A induced osteoclast formation plays a crucial role in bone resorption in rheumatoid arthritis. IL-17A is also believed to play a key role in certain other autoimmune disorders such as multiple sclerosis (Matusevicius et al., Mult. Scler., 5: 101-104 (1999); Kurasawa, K., et al., Arthritis Rheu 43(11):2455-63 (2000)) and psoriasis (Teunissen, M. B., et al., J Invest Dermatol 111(4):645-9 (1998); Albanesi, C., et al., J Invest Dermatol 115(1):81-7 (2000); and Homey, B., et al., J. Immunol. 164(12:6621-32 (2000)).

IL-17A has further been shown, by intracellular signaling, to stimulate Ca.sup.2+influx and a reduction in $[cAMP]_i$ in human macrophages (Jovanovic et al, J. Immunol., 160:3513 (1998)). Fibroblasts treated with IL-17A induce the activation of NFκB, (Yao et al., Immunity, 3:811 (1995), Jovanovic et al., supra), while macrophages treated with it activate NF-κB and mitogen-activated protein kinases (Shalom-Barek et al, J. Biol. Chem., 273:27467 (1998)). Additionally, IL-17A also shares sequence similarity with mammalian cytokine-like factor 7 that is involved in bone and cartilage growth. Other proteins with which IL-17A polypeptides share sequence similarity are human embryo-derived interleukin-related factor (EDIRF) and interleukin-20.

Consistent with IL-17A's wide-range of effects, the cell surface receptor for IL-17A has been found to be widely expressed in many tissues and cell types (Yao et al., Cytokine, 2:794 (1997)). While the amino acid sequence of the human IL-17A receptor (IL-R) (866 amino acids) predicts a protein with a single transmembrane domain and a long, 525 amino acid intracellular domain, the receptor sequence is unique and is not similar to that of any of the receptors from the cytokine/growth factor receptor family. This coupled with the lack of similarity of IL-17A itself to other known proteins indicates that IL-17A and its receptor may be part of a novel family of signaling proteins and receptors. It has been demonstrated that IL-17A activity is mediated through binding to its unique cell surface receptor (designated herein as human IL-17R), wherein previous studies have shown that contacting T cells with a soluble form of the IL-17A receptor polypeptide inhibited T cell proliferation and IL-2 production induced by PHA, concanavalin A and anti-TCR monoclonal antibody (Yao et al., J. Immunol., 155:5483-5486

(1995)). As such, there is significant interest in identifying and characterizing novel polypeptides having homology to the known cytokine receptors, specifically IL-17A receptors.

Interleukin 17A is now recognized as the prototype member of an emerging family of cytokines. The large scale sequencing of the human and other vertebrate genomes has revealed the presence of additional genes encoding proteins clearly related to IL-17A, thus defining a new family of cytokines. There are at least 6 members of the IL-17 family in humans and mice including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F as well as novel receptors IL-17RH1, IL-17RH2, IL-17RH3 and IL-17RH4 (see WO01/46420 published June 28, 2001). One such IL-17 member (designated as IL-17F) has been demonstrated to bind to the human IL-17 receptor (IL-17R) (Yao et al., Cytokine, 9(11):794-800 (1997)). Initial characterization suggests that, like IL-17A, several of these newly identified molecules have the ability to modulate immune function. The potent inflammatory actions that have been identified for several of these factors and the emerging associations with major human diseases suggest that these proteins may have significant roles in inflammatory processes and may offer opportunities for therapeutic intervention.

The gene encoding human IL-17F is located adjacent to IL-17A (Hymowitz, S. G., et al., Embo J, 20(19):5332-41 (2001)). IL-17A and IL-17F share about 44% amino acid identity whereas the other members of the IL-17 family share a more limited 15-27% amino acid identity suggesting that IL-17A and IL-17F form a distinct subgroup within the IL-17 family (Starnes, T., et al., J Immunol. 167(8):4137-40 (2001); Aggarwal, S. and Gurney, A. L., J. Leukoc Biol, 71(1):1-8 (2002)). IL-17F appears to have similar biological actions as IL-17A, and is able to promote the production of IL-6, IL-8, and G-CSF from a wide variety of cells. Similarly to IL-17A, it is able to induce cartilage matrix release and inhibit new cartilage matrix synthesis (see U.S. 2002-0177188-A1 published Nov. 28, 2002). Thus, like IL-17A, IL-17F may potentially contribute to the pathology of inflammatory disorders. It has been reported that both IL-17A and IL-17F are induced in T cells by the action of interleukin 23 (IL-23) (Aggarwal, S., et al., J. Biol. Chem., 278(3):1910-4 (2003)). More specifically, both IL-17A and IL-17F have been implicated as contributing agents to progression and pathology of a variety of inflammatory and autoimmune diseases in humans and mouse models of human diseases. If fact, IL-17A, and to a lesser extent, IL-17F, have been implicated as effector cytokines that trigger inflammatory responses and thereby contribute to a number of autoinflammatory (autoimmune) diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA), and inflammatory bowel diseases

(IBDs). This lineage has been termed Th_{17} and the number of these cells clearly correlates with disease progression and severity in mouse models of human autoimmune diseases. Although the involvement of IL-17A and IL-17F in inflammatory diseases seems clear (see, e.g. Kolls, J. K., A. Linden. Immunity 21: 467-476 (2004)), the target cells for these cytokines have not been identified due in part to the fact that a receptor for IL-17F has not been identified. IL-17A has affinities to a IL-17RA. The amino acid sequence of human IL-17RA is available under NCBI GenBank Accession No. NP_055154.3. To date, at least four additional receptors have been identified in the IL-17R family based on sequence homology to IL-17RA (IL-17Rh1, IL-17Rc, IL-17RD, and IL-17RE) and among them, IL-17Rc has been shown to physically associate with IL-17RA, suggesting that it may be a functional component in the IL-17R complex (Toy, D. et al., J. Immunol. 177: 36-39 (2006)). Recently it has been reported that IL-17Rc is a receptor for both IL-17A and IL-17F (Presnell, et al., J. Immunol. 179(8):5462-73 (2007)).

Inflammation and obesity

An important recent development in our understanding of obesity is the emergence of the concept that inflammation and diabetes are characterized by a state of chronic low-grade inflammation. The basis for this view is that increased circulating levels of several markers of inflammation, both pro-inflammatory cytokines and acute-phase proteins, are elevated in the obese; these markers include IL-6, the TNFα system, C-reactive protein (CRP) and haptoglobin. However, the implications in terms of the site of inflammation itself, whether systemic or local, are unclear.

Insulin resistance, defined as a smaller than expected biological response to a given dose of insulin, is a ubiquitous correlate of obesity. Indeed, many of the pathological consequences of obesity are thought to involve insulin resistance. These include hypertension, hyperlipidemia and, most notably, non-insulin dependent diabetes mellitus (NIDDM). Most NIDDM patients are obese, and a very central and early component in the development of NIDDM is insulin resistance (Moller et al., New Eng. J. Med., 325: 938 (1991)). It has been demonstrated that a post-receptor abnormality develops during the course of insulin resistance, in addition to the insulin receptor downregulation during the initial phases of this disease (Olefsky et al., in Diabetes Mellitus, Rifkin and Porte, Jr., Eds. (Elsevier Science Publishing Co., Inc., New York, ed. 4, 1990), pp. 121-153).

SUMMARY OF THE INVENTION

The present invention is based, at least in part, on the finding that IL-17 family members, and in particular IL-17A and IL-17F, play a role in obesity, insulin resistance and other disorders associated with obesity, such as hyper-lipidemia and the metabolic syndrome, and that IL-17 antagonists, especially IL-17A and IL-17F antagonists, can be used to treat these conditions.

In one aspect, the invention concerns a method of treating an insulin-resistant disorder in a mammal comprising administering to a mammal in need thereof an effective amount of an IL-17A and/or IL-17F antagonist.

In another aspect, the invention concerns a pharmaceutical composition comprising an IL-17A and/or IL-17F antagonist in admixture with a pharmaceutically acceptable excipient, for the treatment of an insulin-resistant disorder.

In a further aspect, the invention concerns the use of an IL-17A and/or IL-17F antagonist in the treatment of an insulin-resistant disorder.

In a still further aspect, the invention concerns a kit for treating an insulin-resistant disorder, said kit comprising: (a) a container comprising an IL-17A and/or IL-17F antagonist; and (b) a label or instructions for administering said antibody to treat said disorder.

In all aspects, in one embodiment, the disorder is selected from the group consisting of non-insulin dependent diabetes mellitus (NIDDM), obesity, ovarian hyperandrogenism, and hypertension. In another embodiment, the disorder is NIDDM or obesity.

In a further embodiment, the mammal is human and the administration is systemic.

In a still further embodiment, the IL-17A and/or IL-17F antagonist is an antibody or a fragment thereof, such as an antibody selected from the group consisting of anti-IL-17A, anti-IL-17F, anti-IL-17A/F, anti-IL-17Rc and anti-IL-17RA antibodies, or a fragment thereof.

Preferably, the antibody is a monoclonal antibody, including chimeric, humanized or human antibodies, bispecific, multispecific or cross-reactive antibodies.

In yet another embodiment, the method includes the administration of an effective amount of an insulin-resistance-treating agent, such as insulin, IGF-1, or a sulfonylurea.

In a further embodiment, the method includes administration of an effective amount of a further agent capable of treating said insulin-resistance disorder, such as Dickkopf-5 (Dkk-5).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence human IL-17A cDNA.

FIG. 2 shows the amino acid sequence (SEQ ID NO:2) of native sequence human IL-17A derived from the coding sequence of SEQ ID NO:1 shown in FIG. 1.

FIG. 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence human IL-17F cDNA.

FIG. 4 shows the amino acid sequence (SEQ ID NO:4) of native sequence human IL-17F derived from the coding sequence of SEQ ID NO:3 shown in FIG.3.

FIG. 5 shows a nucleotide sequence (SEQ ID NO: 5) encoding the native sequence human IL-17 receptor C (IL-17Rc) polypeptide, which is also known as a clone designated "DNA164625-2890."

FIG. 6 shows the amino acid sequence (SEQ ID NO: 6) of the native sequence human IL-17Rc polypeptide (also known as the IL-17RH2 receptor).

FIG. 7 Experimental design of high fat diet (HFD) model study using IL-17Rc KO mice.

FIG. 8 Week 8 results of high fat diet model (HFD) study using IL-17Rc KO mice.

FIGs. 9A and 9B Glucose levels in wild-type and IL-17Rc KO mice in the control group and high fat diet group. IL-17Rc KO mice are resistant to high fat diet (HFD) induced insulin resistance.

FIG. 10 Area under curve at week 10.

FIG. 11 Body weight results.

FIG. 12 Effect of Anti-IL-17 and Anti-IL-17F mAbs on Insulin resistant HF Diet model.

FIG. 13 Glucose tolerance test (GTT) on post 9 week dosing period.

FIG. 14 Ectopic expression of IL-17 A through plasmid DNA injection followed by Glucose tolerance test (GTT). Effect of overexpression of IL-17 on the insulin resistant status assessed through GTT.

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

The term "IL-17" is used to refer generally to members of the IL-17 family, including IL-17A, IL-17, IL-17B, IL-17C, IL-17D, IL-17E, IL-17F, and IL-17A/F. Preferred IL-17s herein are IL-17A, IL-17F, and IL-17A/F.

A "native sequence IL-17 polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding IL-17 polypeptide derived from nature. Such native sequence IL-17 polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence IL-17 polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific IL-17 polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence IL-17 polypeptides disclosed herein are mature or full-length native sequence human IL-17A, IL-17F, and IL-17A/F polypeptides comprising the full-length amino acid sequences shown in Figures 2 and 4 (SEQ ID NOs: 2 and 4). Start and stop codons are shown in bold font and underlined in the figures.

The term "native sequence IL-17Rc polypeptide" or "native sequence IL-17Rc" refers to a polypeptide having the same amino acid sequence as the corresponding IL-17Rc polypeptide derived from nature. Such native sequence IL-17Rc polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence IL-17Rc polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific IL-17Rc polypeptide, naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence IL-17Rc polypeptide disclosed herein full-length native

sequence human IL-17Rc comprising the full-length amino acid shown in Figures 6 (SEQ ID NO: 6).

"Isolated," when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide in situ within recombinant cells, since at least one component of the IL-17 polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

As used herein, "obesity" refers to a condition whereby a mammal has a Body Mass Index (BMI), which is calculated as weight (kg) per height^2 (meters), of at least 25.9. Conventionally, those persons with normal weight have a BMI of 19.9 to less than 25.9. Obesity associated with insulin resistance is specifically included within this definition.

"Insulin resistance" or an "insulin-resistant disorder" or an "insulin-resistant activity" is a disease, condition, or disorder resulting from a failure of the normal metabolic response of peripheral tissues (insensitivity) to the action of exogenous insulin, i.e., it is a condition where the presence of insulin produces a subnormal biological response. In clinical terms, insulin resistance is present when normal or elevated blood glucose levels persist in the face of normal or elevated levels of insulin. It represents, in essence, a glycogen synthesis inhibition, by which either basal or insulin-stimulated glycogen synthesis, or both, are reduced below normal levels. Insulin resistance plays a major role in Type 2 diabetes, as demonstrated by the fact that the hyperglycemia present in Type 2 diabetes can sometimes be reversed by diet or weight loss sufficient, apparently, to restore the sensitivity of peripheral tissues to insulin. The term includes abnormal glucose tolerance, as well as the many disorders in which insulin resistance plays a key role, such as obesity, diabetes mellitus, ovarian hyperandrogenism, and hypertension.

"Diabetes mellitus" refers to a state of chronic hyperglycemia, i.e., excess sugar in the blood, consequent upon a relative or absolute lack of insulin action. There are three basic types of diabetes mellitus, type I or insulin-dependent diabetes mellitus (IDDM), type II or non-insulin-dependent diabetes mellitus (NIDDM), and type A insulin resistance, although type A is relatively rare. Patients with either type I or type II diabetes can become insensitive to the effects of exogenous insulin through a variety of mechanisms. Type A insulin resistance results from either mutations in the insulin receptor gene or defects in post-receptor sites of action critical for glucose metabolism. Diabetic subjects can be easily recognized by the physician, and are characterized by hyperglycemia, impaired glucose tolerance, glycosylated hemoglobin and, in some instances, ketoacidosis associated with trauma or illness.

"Non-insulin dependent diabetes mellitus" or "NIDDM" refers to Type II diabetes. NIDDM patients have an abnormally high blood glucose concentration when fasting and delayed cellular uptake of glucose following meals or after a diagnostic test known as the glucose tolerance test. NIDDM is diagnosed based on recognized criteria (American Diabetes Association, Physician's Guide to Insulin-Dependent (Type I) Diabetes, 1988; American Diabetes Association, Physician's Guide to Non-Insulin-Dependent (Type II) Diabetes, 1988).

Symptoms and complications of diabetes to be treated as a disorder as defined herein include hyperglycemia, unsatisfactory glycemic control, ketoacidosis, insulin resistance, elevated growth hormone levels, elevated levels of glycosylated hemoglobin and advanced glycosylation end-products (AGE), dawn phenomenon, unsatisfactory lipid profile, vascular disease (e.g., atherosclerosis), microvascular disease, retinal disorders (e.g., proliferative diabetic retinopathy), renal disorders, neuropathy, complications of pregnancy (e.g., premature termination and birth defects) and the like. Included in the definition of treatment are such end points as, for example, increase in insulin sensitivity, reduction in insulin dosing while maintaining glycemic control, decrease in HbA1c, improved glycemic control, reduced vascular, renal, neural, retinal, and other diabetic complications, prevention or reduction of the "dawn phenomenon", improved lipid profile, reduced complications of pregnancy, and reduced ketoacidosis.

A "therapeutic composition" or "composition," as used herein, is defined as comprising Dkk-5 and a pharmaceutically acceptable carrier, such as water, minerals, proteins, and other excipients known to one skilled in the art.

The term "mammal" for the purposes of treatment refers to any animal classified as a mammal, including but not limited to, humans, rodents, sport, zoo, pet and domestic or farm animals such as dogs, cats, cattle, sheep, pigs, horses, and non-human primates, such as monkeys. Preferably the rodents are mice or rats. Preferably, the mammal is a human, also called herein a patient.

As used herein, "treating" describes the management and care of a mammal for the purpose of combating any of the diseases or conditions targeted in accordance with the present invention, including, without limitation, insulin resistance, diabetes mellitus, hyperinsulinemia, hypoinsulinemia, or obesity and includes administration to prevent the onset of the symptoms or complications, alleviate the symptoms or complications of, or eliminate the targeted diseases or conditions.

For purposes of this invention, beneficial or desired clinical "treatment" results for reducing insulin resistance include, but are not limited to, alleviation of symptoms associated with insulin resistance, diminishment of the extent of the symptoms of insulin resistance, stabilization (i.e., not worsening) of the symptoms of insulin resistance (e.g., reduction of insulin requirement), increase in insulin sensitivity and/or insulin secretion to prevent islet cell failure, and delay or slowing of insulin-resistance progression, e.g., diabetes progression.

As to obesity, "treatment" generally refers to reducing the BMI of the mammal to less than about 25.9, and maintaining that weight for at least 6 months. The treatment suitably results in a reduction in food or caloric intake by the mammal. In addition, treatment in this context refers to preventing obesity from occurring if the treatment is administered prior to the onset of the obese condition. Treatment includes the inhibition and/or complete suppression of lipogenesis in obese mammals, i.e., the excessive accumulation of lipids in fat cells, which is one of the major features of human and animal obesity, as well as loss of total body weight.

Those "in need of treatment" include mammals already having the disorder, as well as those prone to having the disorder, including those in which the disorder is to be prevented.

An "insulin-resistance-treating agent" is an agent other than an antagonist to IL-17 that is used to treat insulin resistance, such as, for example, Dickkopf-5 (Dkk-5) (see, e.g., U. S. Application Publication No. 2005/0170440), and hypoglycemic agents. Examples of such treating agents include insulin (one or more different insulins); insulin mimetics such as a small-

molecule insulin, e.g., L-783,281; insulin analogs (e.g., HUMALOG® insulin (Eli Lilly Co.), Lys_{B28} insulin, Pro_{B29} insulin, or Asp_{B21} insulin or those described in, for example, U.S. Pat. Nos. 5,149,777 and 5,514,646), or physiologically active fragments thereof; insulin-related peptides (C-peptide, GLP-1, insulin-like growth factor-I (IGE-1), or IGF-1/IGFBP-3 complex) or analogs or fragments thereof; ergoset; pramlintide; leptin; BAY-27-9955; T-1095; antagonists to insulin receptor tyrosine kinase inhibitor; antagonists to TNF-α function; a growth-hormone releasing agent; amylin or antibodies to amylin; an insulin sensitizer, such as compounds of the glitazone family, including those described in U.S. Pat. No. 5,753,681, such as troglitazone, pioglitazone, englitazone, and related compounds; Linalol alone or with Vitamin E (U.S. Pat. No. 6,187,333); insulin-secretion enhancers such as nateglinide (AY-4166), calcium (2S)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionate dihydrate (mitiglinide, KAD-1229), and repaglinide; sulfonylurea drugs, for example, acetohexamide, chlorpropamide, tolazamide, tolbutamide, glyclopyramide and its ammonium salt, glibenclamide, glibomuride, gliclazide, 1-butyl-3-metanilylurea, carbutamide, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcyclamide, glimepiride, etc.; biguanides (such as phenformin, metformin, buformin, etc.); α-glucosidase inhibitors (such as acarbose, voglibose, miglitol, emiglitate, etc.), and such non-typical treatments as pancreatic transplant or autoimmune reagents.

A "weight-loss agent" refers to a molecule useful in treatment or prevention of obesity. Such molecules include, e.g., hormones (catecholamines, glucagon, ACTH, and growth hormone combined with IGF-1); the Ob protein; clofibrate; halogenate; cinchocaine; chlorpromazine; appetite-suppressing drugs acting on noradrenergic neurotransmitters such as mazindol and derivatives of phenethylamine, e.g., phenylpropanolamine, diethylpropion, phentermine, phendimetrazine, benzphetamine, amphetamine, methamphetamine, and phenmetrazine; drugs acting on serotonin neurotransmitters such as fenfluramine, tryptophan, 5-hydroxytryptophan, fluoxetine, and sertraline; centrally active drugs such as naloxone, neuropeptide-Y, galanin, corticotropin-releasing hormone, and cholecystokinin; a cholinergic agonist such as pyridostigmine; a sphingolipid such as a lysosphingolipid or derivative thereof; thermogenic drugs such as thyroid hormone; ephedrine; beta-adrenergic agonists; drugs affecting the gastrointestinal tract such as enzyme inhibitors, e.g. tetrahydrolipostatin, indigestible food such as sucrose polyester, and inhibitors of gastric emptying such as threo-chlorocitric acid or its derivatives; .beta.-adrenergic agonists such as isoproterenol and yohimbine; aminophylline to increase the .beta.-adrenergic-like effects of yohimbine, an α_2-adrenergic blocking drug such as

clonidine alone or in combination with a growth-hormone releasing peptide; drugs that interfere with intestinal absorption such as biguanides such as metformin and phenformin; bulk fillers such as methylcellulose; metabolic blocking drugs such as hydroxycitrate; progesterone; cholecystokinin agonists; small molecules that mimic ketoacids; agonists to corticotropin-releasing hormone; an ergot-related prolactin-inhibiting compound for reducing body fat stores (U.S. Pat. No. 4,783,469 issued Nov. 8, 1988); beta-3-agonists; bromocriptine; antagonists to opioid peptides; antagonists to neuropeptide Y; glucocorticoid receptor antagonists; growth hormone agonists; combinations thereof; etc.

As used herein, "insulin" refers to any and all substances having an insulin action, and exemplified by, for example, animal insulin extracted from bovine or porcine pancreas, semi-synthesized human insulin that is enzymatically synthesized from insulin extracted from porcine pancreas, and human insulin synthesized by genetic engineering techniques typically using E. coli or yeasts, etc. Further, insulin can include insulin-zinc complex containing about 0.45 to 0.9 (w/w)% of zinc, protamine-insulin-zinc produced from zinc chloride, protamine sulfate and insulin, etc. Insulin may be in the form of its fragments or derivatives, e.g., INS-1. Insulin may also include insulin-like substances such as L83281 and insulin agonists. While insulin is available in a variety of types such as super immediate-acting, immediate-acting, bimodal-acting, intermediate-acting, long-acting, etc., these types can be appropriately selected according to the patient's condition.

A "therapeutic composition," as used herein, is defined as comprising an IL-17 (including IL-17A and IL-17F antagonists) antagonist and a pharmaceutically acceptable carrier, such as water, minerals, proteins, and other excipients known to one skilled in the art.

The expressions, "antagonist," "antagonist to IL-17 (A and/or F)," "IL-17 (A and/or F) antagonist" and the like within the scope of the present invention are meant to include any molecule that interferes with the function of IL-17, such as IL-17A and/or IL-17F, or blocks or neutralizes a relevant activity of IL-17 (such as IL-17A and/or F), by whatever means, depending on the indication being treated. It may prevent the interaction between IL-17 (including IL-17 and IL-17F) and one or more of its receptors. Such agents accomplish this effect in various ways. For instance, the class of antagonists that "neutralize" a IL-17 activity will bind to IL-17, or a receptor of IL-17, with sufficient affinity and specificity to interfere with IL-17 as defined below. An antibody "that binds" IL-17, or a receptor of IL-17 (e.g. IL-17Rc), is

one capable of binding that antigen with sufficient affinity such that the antibody is useful as a therapeutic agent in targeting a cell expressing the IL-17 or IL-17 receptor. The term "IL-17 antagonist" is used to refer to any and all of IL-17A, IL-17F and IL-17A/F antagonists.

Included within this group of antagonists are, for example, antibodies directed against IL-17 or portions thereof, reactive with IL-17, or an IL-17 receptor or portions thereof, specifically including antibodies to IL-17A and/or IL-17F and IL-17Rc. The term also includes any agent that will interfere in the overproduction of IL-17A and/or IL-17F or antagonize at least one IL-17 (e.g. IL-17A and/or IL-17F) receptor, such as IL-17Rc. Such antagonists may be in the form of chimeric hybrids, useful for combining the function of the agent with a carrier protein to increase the serum half-life of the therapeutic agent or to confer cross-species tolerance. Hence, examples of such antagonists include bioorganic molecules (e.g., peptidomimetics), antibodies, proteins, peptides, glycoproteins, glycopeptides, glycolipids, polysaccharides, oligosaccharides, nucleic acids, pharmacological agents and their metabolites, transcriptional and translation control sequences, and the like. In a preferred embodiment the antagonist is an antibody having the desirable properties of binding to IL-17A and/or IL-17F, and preventing its interaction with a receptor, preferably IL-17Rc.

The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-IL-17A/F or anti-IL17A or anti-IL-17F monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), corresponding antibody compositions with polyepitopic specificity, polyclonal antibodies, single chain antibodies, and antibody fragments (see below) as long as they exhibit the desired biological or immunological activity.

The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to a H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the α and γ chains and four C_H domains for

μ and ε isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain (C_{H1}). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, e.g., Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, Conn., 1994, page 71 and Chapter 6.

The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated .α, δ, ε, γ, and μ, respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

The term "variable" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and defines specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a .beta.-sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the .beta.-sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L, and around about 1-35 (H1), 50-65 (H2) and 95-102 (H3) in the V_H; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)) and/or those residues from a "hypervariable loop" (e.g. residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L, and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the V_H; Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)).

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. Such monoclonal antibody typically includes an antibody comprising a variable region that binds a target, wherein the antibody was obtained by a process that includes the selection of the antibody from a plurality of antibodies. For example, the selection process can be the selection of a unique clone from a plurality of clones, such as a pool of hybridoma clones, phage clones or recombinant DNA clones. It should be understood that the selected antibody can be further altered, for example, to improve affinity for the target, to humanize the antibody, to improve its production in cell culture, to reduce its immunogenicity *in vivo*, to create a multispecific antibody, etc., and that an antibody comprising the altered variable region sequence is also a monoclonal antibody of this invention. In addition to their specificity, the monoclonal antibody preparations are advantageous in that they are typically uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including the hybridoma method (e.g., Kohler et al., Nature, 256:495 (1975); Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press,

2nd ed. 1988); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681, (Elsevier, N.Y., 1981), recombinant DNA methods (see, e.g., U.S. Patent No. 4,816,567), phage display technologies (see, e.g., Clackson et al., Nature, 352:624-628 (1991); Marks et al., J. Mol. Biol., 222:581-597 (1991); Sidhu et al., J. Mol. Biol. 338(2):299-310 (2004); Lee et al., J.Mol.Biol.340(5):1073-1093 (2004); Fellouse, Proc. Nat. Acad. Sci. USA 101(34):12467-12472 (2004); and Lee et al. J. Immunol. Methods 284(1-2):119-132 (2004) and technologies for producing human or human-like antibodies from animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, e.g., WO98/24893, WO/9634096, WO/9633735, and WO/91 10741, Jakobovits et al., Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggemann et al., Year in Immuno., 7:33 (1993); U.S. Patent Nos. 5,545,806, 5,569,825, 5,591,669 (all of GenPharm); 5,545,807; WO 97/17852, U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016, and Marks et al., Bio/Technology, 10: 779-783 (1992); Lonberg et al., Nature, 368: 856-859 (1994); Morrison, Nature, 368: 812-813 (1994); Fishwild et al., Nature Biotechnology, 14: 845-851 (1996); Neuberger, Nature Biotechnology, 14: 826 (1996); and Lonberg and Huszar, Intern. Rev. Immunol., 13: 65-93 (1995).

The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Pat. No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey, Ape etc), and human constant region sequences.

An "intact" antibody is one which comprises an antigen-binding site as well as a C_L and at least heavy chain constant domains, CH1, CH2 and CH3. The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen

binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (see U.S. Pat. No. 5,641,870, Example 2; Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. In a preferred embodiment, the fragment is "functional," i.e. qualitatively retains the ability of the corresponding intact antibody to bind to the target IL-17A and IL-17F polypeptides and, if the intact antibody also inhibits IL-17A/F biological activity or function, qualitatively retains such inhibitory property as well. Qualitative retention means that the activity in kind is maintained, but the degree of binding affinity and/or activity might differ.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_{H1}). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large $F(ab')_2$ fragment which roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C_{H1} domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific

for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, infra.

The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

"Humanized" forms of non-human (e.g., rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., Nature 321:522-525 (1986); Riechmann et

al., Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992).

The term "multispecific antibody" is used in the broadest sense and specifically covers an antibody comprising a heavy chain variable domain (V_H) and a light chain variable domain (V_L), where the V_HV_L unit has polyepitopic specificity (i.e., is capable of binding to two different epitopes on one biological molecule or each epitope on a different biological molecule). Such multispecific antibodies include, but are not limited to, full length antibodies, antibodies having two or more V_L and V_H domains, antibody fragments such as Fab, Fv, dsFv, scFv, diabodies, bispecific diabodies and triabodies, antibody fragments that have been linked covalently or non-covalently.

"Polyepitopic specificity" refers to the ability to specifically bind to two or more different epitopes on the same or different target(s).

"Monospecific" refers to the ability to bind only one epitope. According to one embodiment the multispecific antibody in an IgG1 form binds to each epitope with an affinity of 5μM to 0.001pM, 3μM to 0.001pM, 1μM to 0.001pM, 0.5μM to 0.001pM or 0.1μM to 0.001pM.

A "cross-reactive antibody" is an antibody which recognizes identical or similar epitopes on more than one antigen. Thus, the cross-reactive antibodies of the present invention recognize identical or similar epitopes present on both IL-17A and IL-17F. In a particular embodiment, the cross-reactive antibody uses the same or essentially the same paratope to bind to both IL-17A and IL-17F. Preferably, the cross-reactive antibodies herein also block both IL-17A and IL-17F function (activity).

The term "paratope" is used herein to refer to the part of an antibody that binds to a target antigen.

A "species-dependent antibody," e.g., a mammalian anti-IL-17A/F" antibody, is an antibody which has a stronger binding affinity for an antigen from a first mammalian species than it has for a homologue of that antigen from a second mammalian species. Normally, the species-dependent antibody "bind specifically" to a human antigen (i.e., has a binding affinity (Kd) value of no more than about 1×10^{-7} M, preferably no more than about 1×10^{-8} M and most preferably no more than about 1×10^{-9} M) but has a binding affinity for a homologue of the antigen from a second non-human mammalian species which is at least about 50 fold, or at least

about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The species-dependent antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody.

An antibody "which binds" an antigen of interest, is one that binds the antigen with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting a cell or tissue expressing the antigen, and does not significantly cross-react with other proteins. In such embodiments, the extent of binding of the antibody to a "non-target" protein will be less than about 10% of the binding of the antibody to its particular target protein as determined by fluorescence activated cell sorting (FACS) analysis or radio immunoprecipitation (RIA). With regard to the binding of an antibody to a target molecule, the term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a Kd for the target of at least about 10^{-4} M, alternatively at least about 10^{-5} M, alternatively at least about 10^{-6} M, alternatively at least about 10^{-7} M, alternatively at least about 10^{-8} M, alternatively at least about 10^{-9} M, alternatively at least about 10^{-10} M, alternatively at least about 10^{-11} M, alternatively at least about 10^{-12} M, or greater. In one embodiment, the term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. In preferred embodiments, the specific binding affinity is at least about 10^{-10} M.

Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effect or functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B

cell receptor); and B cell activation.

"Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies "arm" the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, Annu. Rev. Immunol. 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an in vitro ADCC assay, such as that described in U.S. Pat. No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in a animal model such as that disclosed in Clynes et al. Proc. Natl. Acad. Sci. U.S.A. 95:652-656 (1998).

"Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and Fcγ RIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (see review M. in Daeron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)).

"Human effector cells" are leukocytes which express one or more FcRs and perform

effector functions. Preferably, the cells express at least FcγRIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells may be isolated from a native source, e.g., from blood.

"Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro et al., Immunol. Methods 202:163 (1996), may be performed.

The terms "neutralize", and "neutralize the activity of" are used herein to mean, for example, block, prevent, reduce, counteract the activity of, or make the IL-17 (e.g. IL-17A and/or IL-17F) ineffective by any mechanism. Therefore, the antagonist may prevent a binding event necessary for activation of IL-17.

By "neutralizing antibody" is meant an antibody molecule as herein defined that is able to block or significantly reduce an effector function of IL-17 (including IL-17A and/or IL-17F). For example, a neutralizing antibody may inhibit or reduce the ability of IL-17 (e.g. IL-17A and/or IL-17F) to interact with an IL-17 receptor, such as IL-17Rc. Alternatively, the neutralizing antibody may inhibit or reduce the ability of IL-17 to block the IL-17 receptor signaling pathway. The neutralizing antibody may also immunospecifically bind to the IL-17 in an immunoassay for IL-17 activity. It is a characteristic of the "neutralizing antibody" of the invention that it retain its functional activity in both in vitro and in vivo situations.

B. Detailed description

1. Therapeutic uses

Insulin resistance is a condition where the presence of insulin produces a subnormal biological response. In clinical terms, insulin resistance is present when normal or elevated blood glucose levels persist in the face of normal or elevated levels of insulin. It represents, in essence, a glycogen synthesis inhibition, by which either basal or insulin-stimulated glycogen synthesis, or both, are reduced below normal levels. Insulin resistance plays a major role in Type

2 diabetes, as demonstrated by the fact that the hyperglycemia present in Type 2 diabetes can sometimes be reversed by diet or weight loss sufficient, apparently, to restore the sensitivity of peripheral tissues to insulin.

The present invention concerns the treatment of insulin resistance or type 2 diabetes by administration of an IL-17A and/or IL-17F antagonist. As discussed earlier, IL-17A and/or IL-17F antagonist may be any molecule that interferes with the function of IL-17A and/or IL-17F, or blocks or neutralizes a relevant activity of IL-17A and/or F, by whatever means, depending on the indication being treated. It may prevent the interaction between IL-17A and/or IL-17F and one or more of its receptors, especially IL-17Rc. Such agents accomplish this effect in various ways. For instance, the class of antagonists that neutralize an IL-17A and/or IL-17F activity will bind to IL-17A and/or IL-17F, or a receptor of IL-17A and/or IL-17F, especially IL-17Rc, with sufficient affinity and specificity to interfere with IL-17A and/or IL-17F.

2. Administration and formulations

The IL-17 antagonist may be administered by any suitable route, including a parenteral route of administration such as, but not limited to, intravenous (IV), intramuscular (IM), subcutaneous (SC), and intraperitoneal (IP), as well as transdermal, buccal, sublingual, intrarectal, intranasal, and inhalant routes. IV, IM, SC, and IP administration may be by bolus or infusion, and in the case of SC, may also be by slow-release implantable device, including, but not limited to pumps, slow-release formulations, and mechanical devices. Preferably, administration is systemic.

One specifically preferred method for administration of IL-17 antagonist is by subcutaneous infusion, particularly using a metered infusion device, such as a pump. Such pump can be reusable or disposable, and implantable or externally mountable. Medication infusion pumps that are usefully employed for this purpose include, for example, the pumps disclosed in U.S. Pat. Nos. 5,637,095; 5,569,186; and 5, 527,307. The compositions can be administered continaully from such devices, or intermittently.

Therapeutic formulations of IL-17 antagonists suitable for storage include mixtures of the antagonist having the desired degree of purity with pharmaceutically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed,

and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEENT™, PLURONICS™ or polyethylene glycol (PEG). Preferred lyophilized anti-IL-17 antibody formulations are described in WO 97/04801. These compositions comprise antagonist to IL-17 containing from about 0.1 to 90% by weight of the active antagonist, preferably in a soluble form, and more generally from about 10 to 30%.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, supra.

The IL-17A ad/or IL-17F antagonists, such as anti-IL-17 antibodies disclosed herein may 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); U.S. Pat. Nos. 4,485,045 and 4,544,545; and WO97/38731 published Oct. 23, 1997. Liposomes with enhanced circulation time are disclosed in U.S. Pat. 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.

Sustained-release preparations may 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 y 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.

Any of the specific antagonists can be joined to a carrier protein to increase the serum half-life of the therapeutic antagonist. For example, a soluble immunoglobulin chimera, such as described herein, can be obtained for each specific IL-17 antagonist or antagonistic portion thereof, as described in U.S. Pat. No. 5,116,964. The immunoglobulin chimera are easily purified through IgG-binding protein A-Sepharose chromatography. The chimera have the ability to form an immunoglobulin-like dimer with the concomitant higher avidity and serum half-life.

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

The formulation herein may 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. Also, such active compound can be administered separately to the mammal being treated.

For example, it may be desirable to further provide an insulin-resistance-treating agent for those indications. In addition, type 2 diabetics that fail to respond to diet and weight loss may respond to therapy with sulfonylureas along with the IL-17 antagonist. The class of sulfonylurea drugs includes acetohexamide, chlorpropamide, tolazamide, tolbutamide, glibenclaminde, glibomuride, gliclazide, glipizide, gliquidone and glymidine. Other agents for this purpose include an autoimmune reagent, an insulin sensitizer, such as compounds of the glitazone family,

including those described in U.S. Pat. No. 5,753,681, such as troglitazone, pioglitazone, englitazone, and related compounds, antagonists to insulin receptor tyrosine kinase inhibitor (U.S. Pat. Nos. 5,939,269 and 5,939,269), IGF-1/IGFBP-3 complex (U.S. Pat. No. 6,040,292), antagonists to TNF-alpha function (U.S. Pat. No. 6,015,558), growth hormone releasing agent (U.S. Pat. No. 5,939,387), and antibodies to amylin (U.S. Pat. No. 5,942,227). Other compounds that can be used include insulin (one or more different insulins), insulin mimetics such as a small-molecule insulin, insulin analogs as noted above or physiologically active fragments thereof, insulin-related peptides as noted above, or analogs or fragments thereof. Agents are further specified in the definition above.

For treating hypoinsulinemia, for example, insulin may be administered together or separately from the antagonist to IL-17.

Such additional molecules are suitably present or administered in combination in amounts that are effective for the purpose intended, typically less than what is used if they are administered alone without the antagonist to IL-17. If they are formulated together, they may be formulated in the amounts determined according to, for example, the type of indication, the subject, the age and body weight of the subject, current clinical status, administration time, dosage form, administration method, etc. For instance, a concomitant drug is used preferably in a proportion of about 0.0001 to 10,000 weight parts relative to one weight part of the antagonist to IL-17 herein.

Use of the antagonist to IL-17 in combination with insulin enables reduction of the dose of insulin as compared with the dose at the time of administration of insulin alone. Therefore, risk of blood vessel complication and hypoglycemia induction, both of which may be problems with large amounts of insulin administration, is low. For administration of insulin to an adult diabetic patient (body weight about 50 kg), for example, the dose per day is usually about 10 to 100 U (Units), preferably 10 to 80 U, but this may be less as determined by the physician. For administration of insulin secretion enhancers to the same type of patient, for example, the dose per day is preferably about 0.1 to 1000 mg, more preferably about 1 to 100 mg. For administration of biguanides to the same type of patient, for example, the dose per day is preferably about 10 to 2500 mg, more preferably about 100 to 1000 mg. For administration of a-glucosidase inhibitors to the same type of patient, for example, the dose per day is preferably about 0.1 to 400 mg, more preferably about 0.6 to 300 mg. Administration of ergoset,

pramlintide, leptin, BAY-27-9955, or T-1095 to such patients can be effected at a dose of preferably about 0.1 to 2500 mg, more preferably about 0.5 to 1000 mg. All of the above doses can be administered once to several times a day.

The IL-17 antagonist may also be administered together with a suitable non-drug treatment for insulin resistance such as a pancreatic transplant.

The dosages of antagonist administered to an insulin-resistant or hypoinsulinemic mammal will be determined by the physician in the light of the relevant circumstances, including the condition of the mammal, the type of antagonist, the type of indication, and the chosen route of administration. The dosage is preferably at a sufficiently low level as not to cause weight gain to any significant degree, and the physician can determine that level. Glitazones approved for the treatment of human Type 2 diabetes (rosiglitazone/Avandia and pioglitazone/Actos) cause some weight gain, yet they are used despite the side effects because they have proven to be beneficial by their therapeutic index. The dosage ranges presented herein are not intended to limit the scope of the invention in any way. A "therapeutically effective" amount for purposes herein for hypoinsulinemia and insulin resistance is determined by the above factors, but is generally about 0.01 to 100 mg/kg body weight/day. The preferred dose is about 0.1-50 mg/kg/day, more preferably about 0.1 to 25 mg/kg/day. More preferred still, when the IL-17 antagonist is administered daily, the intravenous or intramuscular dose for a human is about 0.3 to 10 mg/kg of body weight per day, more preferably, about 0.5 to 5 mg/kg. For subcutaneous administration, the dose is preferably greater than the therapeutically-equivalent dose given intravenously or intramuscularly. Preferably, the daily subcutaneous dose for a human is about 0.3 to 20 mg/kg, more preferably about 0.5 to 5 mg/kg for both indications.

The invention contemplates a variety of dosing schedules. The invention encompasses continuous dosing schedules, in which IL-17 antagonist is administered on a regular (daily, weekly, or monthly, depending on the dose and dosage form) basis without substantial breaks. Preferred continuous dosing schedules include daily continuous infusion, where IL-17 antagonist is infused each day, and continuous bolus administration schedules, where IL-17 antagonist is administered at least once per day by bolus injection or inhalant or intranasal routes. The invention also encompasses discontinuous dosing schedules. The exact parameters of discontinuous administration schedules will vary according to the formulation, method of delivery, and clinical needs of the mammal being treated. For example, if the IL-17 antagonist is

administered by infusion, administration schedules may comprise a first period of administration followed by a second period in which IL-17 antagonist is not administered that is greater than, equal to, or less than the first period.

Where the administration is by bolus injection, especially bolus injection of a slow-release formulation, dosing schedules may also be continuous in that IL-17 antagonist is administered each day, or may be discontinuous, with first and second periods as described above.

Continuous and discontinuous administration schedules by any method also include dosing schedules in which the dose is modulated throughout the first period, such that, for example, at the beginning of the first period, the dose is low and increased until the end of the first period, the dose is initially high and decreased during the first period, the dose is initially low, increased to a peak level, then reduced towards the end of the first period, and any combination thereof.

The effects of administration of IL-17 antagonist on insulin resistance can be measured by a variety of assays known in the art. Most commonly, alleviation of the effects of diabetes will result in improved glycemic control (as measured by serial testing of blood glucose), reduction in the requirement for insulin to maintain good glycemic control, reduction in glycosylated hemoglobin, reduction in blood levels of advanced glycosylation end-products (AGE), reduced "dawn phenomenon", reduced ketoacidosis, and improved lipid profile. Alternately, administration of IL-17 antagonist can result in a stabilization of the symptoms of diabetes, as indicated by reduction of blood glucose levels, reduced insulin requirement, reduced glycosylated hemoglobin and blood AGE, reduced vascular, renal, neural and retinal complications, reduced complications of pregnancy, and improved lipid profile.

The blood sugar lowering effect of the IL-17 antagonist can be evaluated by determining the concentration of glucose or Hb (hemoglobin)A_{1c} in venous blood plasma in the subject before and after administration, and then comparing the obtained concentration before administration and after administration. HbA_{1c} means glycosylated hemoglobin, and is gradually produced in response to blood glucose concentration. Therefore, HbA_{1c} is thought important as an index of blood sugar control that is not easily influenced by rapid blood sugar changes in diabetic patients.

Evidence of treating hypoinsulinemia is shown, for example, by an increase in circulating levels of insulin in the patient.

The dosing for muscle repair and regeneration is typically about 0.01 to 100 mg/kg body weight, more preferably 1 to 10 mg/kg depending on the patient's condition, the specific type of muscle repair desired, etc. The dosing schedule is in accordance with the standard schedule used by a clinician in this area. Evidence of muscle repair or regeneration is shown by various measurement tests well known in the art, including assaying for proliferation and differentiation of muscle cells and a polymerase chain reaction test (see, e.g., Best et al., J. Orthop. Res., 19: 565-572 (2001), which provides an analysis of changes in mRNA levels of myoblast- and fibroblast-derived gene products in healing rabbit skeletal muscle using quantitative reverse transcription-polymerase chain reaction).

3. Articles of manufacture and kits

The invention also provides kits for the treatment of insulin resistance and hypoinsulinemia, and for repair and regeneration of muscle. The kits of the invention comprise one or more containers of IL-17 antagonist, preferably antibody, in combination with a set of instructions, generally written instructions, relating to the use and dosage of IL-17 antagonist for the treatment of insulin resistance or hypoinsulinemia, or for any other target disease associated with insulin resistance. The instructions included with the kit generally include information as to dosage, dosing schedule, and route of administration for the treatment of the target disease, such as insulin-resistant or hypoinsulinemic disorder. The containers of IL-17 antagonist may be unit doses, bulk packages (e.g., multi-dose packages), or sub-unit doses.

The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an IL-17 antagonist of the invention. The label or package insert indicates that the composition is used for treating the particular condition. The label or package insert will further comprise instructions for administering the antibody composition to the patient. Articles of manufacture and kits comprising combinatorial therapies described herein are also contemplated.

Package insert refers to instructions customarily included in commercial packages of therapeutic products that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products

Additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

4. Preparation of antibodies

Monoclonal antibodies

Monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., Nature, 256:495 (1975), or may be made by recombinant DNA methods (U.S. Pat. No. 4,816,567). In the hybridoma method, a mouse or other appropriate host animal, such as a hamster or macaque monkey, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized in vitro. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)).

The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma 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 myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk

Institute Cell Distribution Center, San Diego, Calif. USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection, Rockville, Md. USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); Brodeur et al, Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subloned by limiting dilution procedures and grown by standard methods (Goding, MonoclonalAntibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown in vivo as ascites tumors in an animal.

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

DNA encoding the monoclonal antibodies is 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 the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, 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. Recombinant production of antibodies will be described in more detail below.

In a further embodiment, antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., Nature, 348:552-554 (1990).

Clackson et al., Nature, 352:624-628 (1991) and Marks etal., J. Mol. Biol., 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., Bio/Technology, 10:779-783 (1992)), as well as combinatorial infection and in vivo recombination as a strategy for constructing very large phage libraries (Waterhouse et al., Nuc. Acids. Res., 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Pat. No. 4,816,567; Morrison, et al., Proc. Natl. Acad. Sci. USA, 81:6851 (1984)), or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

Typically such non-immunoglobulin polypeptides are substituted for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

Humanized and human antibodies

A humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species.

In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework (FR) for the humanized antibody (Sims et al., J. Immunol., 151:2296 (1993); Chothia et al., J. Mol. Biol., 196:901 (1987)). Another method uses a particular framework derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., Proc. Natl. Acad Sci. USA, 89:4285 (1992); Presta et al., J. Immnol., 151:2623 (1993)).

It is further important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding.

Alternatively, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J.sub.H) gene in chimeric and

germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits et al, Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggermann et al., Year in Immuno., 7:33 (1993); and Duchosal et al. Nature 355:258 (1992). Human antibodies can also be derived from phage-display libraries (Hoogenboom et al, J. Mol. Biol., 227:381 (1991); Marks et al, J. MoL Biol., 222:581-597 (1991); Vaughan et al. Nature Biotech 14:309 (1996)). Generation of human antibodies from antibody phage display libraries is further described below.

Antibody Fragments

Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto et al., Journal of Biochemical and Biophysical Methods 24:107-117 (1992) and Brennan et al., Science, 229:81 (1985)). However, these fragments can now be produced directly by recombinant host cells. For example, the antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from E. coli and chemically coupled to form $F(ab')_2$ fragments (Carter et al., Bio/Technology 10:163-167 (1992)). In another embodiment as described in the example below, the $F(ab')_2$ is formed using the leucine zipper GCN4 to promote assembly of the $F(ab')_2$ molecule. According to another approach, $F(ab')_2$ fragments can be isolated directly from recombinant host cell culture. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185.

Multispecific Antibodies

Multispecific antibodies have binding specificities for at least two different epitopes, where the epitopes are usually from different antigens. While such molecules normally will only bind two different epitopes (i.e. bispecific antibodies, BsAbs), antibodies with additional specificities such as trispecific antibodies are encompassed by this expression when used herein. Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the coexpression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., Nature, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light

chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., EMBO J., 10:3655-3659 (1991). According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are 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. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. 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 WO96/27011, 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 domain 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 include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Pat. No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Pat. No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also 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.

Fab'-SH fragments can also be directly recovered from E. coli, and can be 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.

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. Nati. 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 (VH) connected to a light-chain variable domain (VL) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the VH and VL domains of one fragment are forced to pair with the complementary VL and VH 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. Tuft et al. J. Immunol. 147: 60 (1991).

Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance the effectiveness of the antibody. For example cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may 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, B. J. Immunol. 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctonal cross-linkers as described in Wolff et al. Cancer Research 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al Anti-Cancer Drug Design 3:219-230 (1989).

Antibody-Salvage Receptor Binding Epitope Fusions.

In certain embodiments of the invention, it may be desirable to use an antibody fragment, rather than an intact antibody. In this case, it may be desirable to modify the antibody fragment in order to increase its serum half life. This may be achieved, for example, by incorporation of a salvage receptor binding epitope into the antibody fragment (e.g. by mutation of the appropriate region in the antibody fragment or by incorporating the epitope into a peptide tag that is then fused to the antibody fragment at either end or in the middle, e.g., by DNA or peptide synthesis).

The salvage receptor binding epitope preferably constitutes a region wherein any one or

more amino acid residues from one or two loops of a Fc domain are transferred to an analogous position of the antibody fragment. Even more preferably, three or more residues from one or two loops of the Fc domain are transferred. Still more preferred, the epitope is taken from the CH2 domain of the Fc region (e.g., of an IgG) and transferred to the CH1, CH3, or V.sub.H region, or more than one such region, of the antibody. Alternatively, the epitope is taken from the CH2 domain of the Fc region and transferred to the CL region or VL region, or both, of the antibody fragment.

Other Covalent Modifications of Antibodies

Covalent modifications of antibodies are included within the scope of this invention. They may be made by chemical synthesis or by enzymatic or chemical cleavage of the antibody, if applicable. Other types of covalent modifications of the antibody are introduced into the molecule by reacting targeted amino acid residues of the antibody with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues. Examples of covalent modifications are described in U.S. Pat. No. 5,534,615, specifically incorporated herein by reference. A preferred type of covalent modification of the antibody comprises linking the antibody to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

Generation of Antibodies From Synthetic Antibody Phage Libraries

In a preferred embodiment, the invention provides a method for generating and selecting novel antibodies using a unique phage display approach. The approach involves generation of synthetic antibody phage libraries based on single framework template, design of sufficient diversities within variable domains, display of polypeptides having the diversified variable domains, selection of candidate antibodies with high affinity to target the antigen, and isolation of the selected antibodies.

Details of the phage display methods can be found, for example, WO03/102157 published December 11, 2003, the entire disclosure of which is expressly incorporated herein by reference.

In one aspect, the antibody libraries used in the invention can be generated by mutating the solvent accessible and/or highly diverse positions in at least one CDR of an antibody variable domain. Some or all of the CDRs can be mutated using the methods provided herein. In some

embodiments, it may be preferable to generate diverse antibody libraries by mutating positions in CDRH1, CDRH2 and CDRH3 to form a single library or by mutating positions in CDRL3 and CDRH3 to form a single library or by mutating positions in CDRL3 and CDRH1, CDRH2 and CDRH3 to form a single library.

A library of antibody variable domains can be generated, for example, having mutations in the solvent accessible and/or highly diverse positions of CDRH1, CDRH2 and CDRH3. Another library can be generated having mutations in CDRL1, CDRL2 and CDRL3. These libraries can also be used in conjunction with each other to generate binders of desired affinities. For example, after one or more rounds of selection of heavy chain libraries for binding to a target antigen, a light chain library can be replaced into the population of heavy chain binders for further rounds of selection to increase the affinity of the binders.

Preferably, a library is created by substitution of original amino acids with variant amino acids in the CDRH3 region of the variable region of the heavy chain sequence. The resulting library can contain a plurality of antibody sequences, wherein the sequence diversity is primarily in the CDRH3 region of the heavy chain sequence.

In one aspect, the library is created in the context of the humanized antibody 4D5 sequence, or the sequence of the framework amino acids of the humanized antibody 4D5 sequence. Preferably, the library is created by substitution of at least residues 95-100a of the heavy chain with amino acids encoded by the *DVK* codon set, wherein the *DVK* codon set is used to encode a set of variant amino acids for every one of these positions. An example of an oligonucleotide set that is useful for creating these substitutions comprises the sequence $(DVK)_7$. In some embodiments, a library is created by substitution of residues 95-100a with amino acids encoded by both *DVK and NNK* codon sets. An example of an oligonucleotide set that is useful for creating these substitutions comprises the sequence $(DVK)_6$ *(NNK)*. In another embodiment, a library is created by substitution of at least residues 95-100a with amino acids encoded by both *DVK* and *NNK* codon sets. An example of an oligonucleotide set that is useful for creating these substitutions comprises the sequence $(DVK)_5$ *(NNK)*. Another example of an oligonucleotide set that is useful for creating these substitutions comprises the sequence $(NNK)_6$. Other examples of suitable oligonucleotide sequences can be determined by one skilled in the art according to the criteria described herein.

In another embodiment, different CDRH3 designs are utilized to isolate high affinity

binders and to isolate binders for a variety of epitopes. The range of lengths of CDRH3 generated in this library is 11 to 13 amino acids, although lengths different from this can also be generated. H3 diversity can be expanded by using *NNK, DVK and NVK* codon sets, as well as more limited diversity at N and/or C-terminal.

Diversity can also be generated in CDRH1 and CDRH2. The designs of CDR-H1 and H2 diversities follow the strategy of targeting to mimic natural antibodies repertoire as described with modification that focus the diversity more closely matched to the natural diversity than previous design.

For diversity in CDRH3, multiple libraries can be constructed separately with different lengths of H3 and then combined to select for binders to target antigens. The multiple libraries can be pooled and sorted using solid support selection and solution sorting methods as described previously and herein below. Multiple sorting satrategies may be employed. For example, one variation involves sorting on target bound to a solid, followed by sorting for a tag that may be present on the fusion polypeptide (eg. anti-gD tag) and followed by another sort on target bound to solid. Alternatively, the libraries can be sorted first on target bound to a solid surface, the eluted binders are then sorted using solution phase binding with decreasing concentrations of target antigen. Utilizing combinations of different sorting methods provides for minimization of selection of only highly expressed sequences and provides for selection of a number of different high affinity clones.

High affinity binders for the target antigen can be isolated from the libraries. Limiting diversity in the H1/H2 region decreases degeneracy about 10^4 to 10^5 fold and allowing more H3 diversity provides for more high affinity binders. Utilizing libraries with different types of diversity in CDRH3 (eg. utilizing DVK or NVT) provides for isolation of binders that may bind to different epitopes of a target antigen.

Of the binders isolated from the pooled libraries as described above, it has been discovered that affinity may be further improved by providing limited diversity in the light chain. Light chain diversity is generated in this embodiment as follows in CDRL1: amino acid position 28 is encoded by RDT; amino acid position 29 is encoded by RKT; amino acid position 30 is encoded by RVW; amino acid position 31 is encoded by ANW; amino acid position 32 is encoded by THT; optionally, amino acid position 33 is encoded by CTG ; in CDRL2: amino acid position 50 is encoded by KBG; amino acid position 53 is encoded by AVC; and optionally,

amino acid position 55 is encoded by GMA ; in CDRL3: amino acid position 91 is encoded by TMT or SRT or both; amino acid position 92 is encoded by DMC; amino acid position 93 is encoded by RVT; amino acid position 94 is encoded by NHT; and amino acid position 96 is encoded by TWT or YKG or both.

In another embodiment, a library or libraries with diversity in CDRH1, CDRH2 and CDRH3 regions is generated. In this embodiment, diversity in CDRH3 is generated using a variety of lengths of H3 regions and using primarily codon sets *XYZ and NNK or NNS*. Libraries can be formed using individual oligonucleotides and pooled or oligonucleotides can be pooled to form a subset of libraries. The libraries of this embodiment can be sorted against target bound to solid. Clones isolated from multiple sorts can be screened for specificity and affinity using ELISA assays. For specificity, the clones can be screened against the desired target antigens as well as other nontarget antigens. Those binders to the target antigen can then be screened for affinity in solution binding competition ELISA assay or spot competition assay. High affinity binders can be isolated from the library utilizing *XYZ* codon sets prepared as described above. These binders can be readily produced as antibodies or antigen binding fragments in high yield in cell culture.

In some embodiments, it may be desirable to generate libraries with a greater diversity in lengths of CDRH3 region. For example, it may be desirable to generate libraries with CDRH3 regions ranging from about 7 to 19 amino acids.

High affinity binders isolated from the libraries of these embodiments are readily produced in bacterial and eukaryotic cell culture in high yield. The vectors can be designed to readily remove sequences such as gD tags, viral coat protein component sequence, and/or to add in constant region sequences to provide for production of full length antibodies or antigen binding fragments in high yield.

A library with mutations in CDRH3 can be combined with a library containing variant versions of other CDRs, for example CDRL1, CDRL2, CDRL3, CDRH1 and/or CDRH2. Thus, for example, in one embodiment, a CDRH3 library is combined with a CDRL3 library created in the context of the humanized 4D5 antibody sequence with variant amino acids at positions 28, 29, 30,31, and/or 32 using predetermined codon sets. In another embodiment, a library with mutations to the CDRH3 can be combined with a library comprising variant CDRH1 and/or CDRH2 heavy chain variable domains. In one embodiment, the CDRH1 library is created with

the humanized antibody 4D5 sequence with variant amino acids at positions 28, 30, 31, 32 and 33. A CDRH2 library may be created with the sequence of humanized antibody 4D5 with variant amino acids at positions 50, 52, 53, 54, 56 and 58 using the predetermined codon sets.

The foregoing written description is considered to be sufficient to enable one skilled in the art to practice the invention. The following Examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

Commercially available reagents referred to in the Examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following Examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA. Unless otherwise noted, the present invention uses standard procedures of recombinant DNA technology, such as those described hereinabove and in the following textbooks: Sambrook *et al., supra*; Ausubel *et al.,* Current Protocols in Molecular Biology (Green Publishing Associates and Wiley Interscience, N.Y., 1989); Innis *et al.,* PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc.: N.Y., 1990); Harlow *et al.,* Antibodies: A Laboratory Manual (Cold Spring Harbor Press: Cold Spring Harbor, 1988); Gait, Oligonucleotide Synthesis (IRL Press: Oxford, 1984); Freshney, Animal Cell Culture, 1987; Coligan *et al.,* Current Protocols in Immunology, 1991.

Further details of the invention are provided in the following non-limiting examples.

All references cited throughout the disclosure are hereby expressly incorporated by reference in their entirety.

Example 1

Role of Il-17 family members in diabetes and insulin resistance.
IL-17Rc KO mice and High Fat diet model study

8 weeks old male IL-17Rc (UNQ6118.KO.lex) Knockout and littermate wild-type (WT) control mice were either fed with regular Chow diet or 60% High fat diet (HFD).

GROUP 1: IL-17Rc Knockout (KO) mice on High fat diet (5 animals)

GROUP 2: IL-17Rc, WT littermate control on High fat diet (5 animals)

GROUP 3: IL-17Rc KO mice on regular Diet (3 animals)

GROUP 4: IL-17Rc WT littermate control on Regular Diet (3 animals).

The experimental design is shown in Figure 7.

The mice were subjected to Glucose Tolerance Test (GTT) to access their Insulin Resistance status.

GTT was performed using the following method.

Blood glucose and insulin measurements: Blood samples were obtained by saphenous vein bleeds, and analyzed for glucose concentration immediately using a glucometer (OneTouch Glucometer made by Lifescan, USA). Serum Insulin was measured using ELISA method.

Glucose Tolerance Test (GTT): Following overnight fasting (14hrs), Animals were tested in the morning, at 9:00 am. Blood glucose was measured on samples obtained from saphenous vein bleeds before the intraperitoneal injection of glucose at 1.5 mg/gram body weight of each animal, as well as at 30, 60, 120 and 150 minutes after glucose administration. The values were calculated as mg/dL of glucose.

The GTT was performed for base line (before they put on High fat Diet) as well as Week 8, Week 10, Week 12 and Week 14 following High fat diet group. Regular Chow diet fed mice were used as control groups. The rest of the conditions were similar in both Knockout and Wild Type (WT) littermate control mice.

In addition to GTT total body weight of the animal as well as fasting serum Insulin and Glucose levels were monitored every week.

The results are shown in Figures 8-11.

While IL-17Rc WT littermate control mice showed significant weight gain and developed insulin resistant phenotype, IL-17Rc Knockout mice were significantly leaner and

cleared glucose much better than their WT littermate controls. Even after feeding with High fat diet for more than 12 weeks, knockout mice did not gain weight. Both groups showed similar level of fasting circulating insulin levels. No significant difference was observed between KO and WT mice in the control diet fed groups.

In addition to the experiment described above using IL-17 Rc KO mice TWO separate lineS of study were undertaken to address the role of proinflammatory cytokines Il-17A and IL-17F in diabetes and insulin resistance.

Example 2

Effect of Anti-IL-17 and Anti-IL-17F mAbs on Insulin resistant High Fat Diet model mice.

The purpose of this study was to investigate the efficacy of Anti-Il-17 and Anti-IL-17F mAbs in preventive and established insulin resistance model and to compare with the therapeutic effect of muTNFRII-Fc.

Experimental design and groups:

Group.1: Ragweed 6 mg/kg in 100ul saline ip 3 times/week for 10 weeks (n=10).

Group.2: MuTNFRII-IgG2a 4 mg/kg in 100 µl saline 3 times/week for 10 weeks (n=10).

Group.3: MuAnti-IL-17 6 mg/kg in 100ul saline ip 3 times/wk for 10 weeks (n=10).

Group.4: MuAnti-IL-17+MuAnti-IL-17F mAb 6mg/kg in 100 µl saline ip 3 times/wk for 10 weeks (n=10).

Group.5: MuTNFRII-Fc 4.mg/kg=MuAnti-IL-17 6.mg/kg+MuAnti-IL17FmAb 6.mg/kg in 18 weeks and 24 weeks (10 animals).

. All groups were subjected to high fat diet feeding. In order to assess the insulin resistance status of the mice glucose tolerance test (GTT) was performed every 2 weeks following HFD and antibody dosing.

The protocol is illustrated in Figure 12. The effect of the anti-IL-17A and anti-IL-17F

MAbs on glucose tolerance after 9 weeks of dosing is shown in Figure 13.

Example 3

Effect of over expression of IL-17 on the Insulin resistant status assessed through GTT

The study was based on hydrodynamic tail vein (HTV) injection of plasmid DNA for the expression of native murine IL-17A and IL-17F proteins in normal and High fat diet fed mice to express high level of pro-inflammatory cytokines murine IL-17A and IL-17F in mice for studying its role in Insulin resistance.

Group 1: no plasmid

Group 2: pRK vector alone

Group3: pRK-IL-17A

Group 4: pRK-IL-17F

Within each group 5 sub-groups of mice were injected to draw blood at various time points (0 h, 2 h, 6 h, 24 h, and 72 h post DNA ingestion) to measure the circulating cytokine levels in serum. Once this was established, IL-17A and Il-17F were overexpressed in high fat diet (HFD) mice to access the change in insulin resistance status.

Tail vein injection experiments:

1) DNA construct (pRK vector or pRK-IL-17A and pRK-IL-17F) were diluted in saline (Ringer's preferred) to a concentration which will yield a final dose of 50 µg/mouse/injection.

2) Each mouse was be injected intravenously in the tail vein with approximately 1.6 ml of the solution containing DNA in saline or Ringer's.

3) Doses were administered as a bolus intravenous injection (tail vein) over a period of 4-5 seconds (8 seconds maximum) for maximum DNA uptake.

The results are shown in Figure 14. A) Eight weeks old c57BL/6 mice were injected with 50 ug of Plasmid DNA (pRK-IL-17A) or pRK vector alone. 48 hrs later serum was collected from both groups and Il-17 level in the serum was measured by ELISA. B) Three

groups of mice were fasted O/N and subjected to ip GTT and results are plotted over time following glucose injection. (*p>0.05).

While the present invention has been described with reference to what are considered to be the specific embodiments, it is to be understood that the invention is not limited to such embodiments. To the contrary, the invention is intended to cover various modifications and equivalents included within the spirit and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method of treating an insulin-resistant disorder in a mammal comprising administering to a mammal in need thereof an effective amount of an IL-17A and/or IL-17F antagonist.

2. The method of claim 1 wherein the disorder is selected from the group consisting of non-insulin dependent diabetes mellitus (NIDDM), obesity, ovarian hyperandrogenism, and hypertension.

3. The method of claim 2 wherein the disorder is NIDDM or obesity.

4. The method of claim 1 wherein the mammal is human and the administration is systemic.

5 The method of claim 1 wherein the IL-17A and/or IL-17F antagonist is an antibody or a fragment thereof.

6. The method of claim 5 wherein the antibody is an antibody selected from the group consisting of anti-IL-17A, anti-IL-17F, anti-IL-17A/F, anti-IL-17Rc and anti-IL-17RA antibodies.

7. The method of claim 6 wherein the antibody is a monoclonal antibody.

8. The method of claim 7 wherein the antibody is a chimeric, humanized or human antibody.

9. The method of claim 8 wherein the antibody is a bispecific, multispecific or cross-reactive antibody.

10. The method of claim 9 further comprising administering an effective amount of an insulin-resistance-treating agent.

11. The method of claim 10 wherein the insulin-resistance-treating agent is insulin, IGF-1, or a sulfonylurea.

12. The method of claim 10 further comprising an effective amount of a further agent capable of treating said insulin-resistance disorder.

13. The method of claim 12 wherein the further agent is Dickkopf-5 (Dkk-5).

14. A pharmaceutical composition comprising an IL-17A and/or IL-17F antagonist in admixture with a pharmaceutically acceptable excipient, for the treatment of an insulin-resistant disorder.

15. The pharmaceutical composition of claim 14 wherein the IL-17A and/or IL-17F antagonist is an antibody or a fragment thereof.

16. The pharmaceutical composition of claim 15 wherein the antibody is an antibody selected from the group consisting of anti-IL-17A, anti-IL-17F, anti-IL-17A/F, anti-IL-17Rc and anti-IL-17RA antibodies.

17. The pharmaceutical composition of claim 16 wherein the antibody is a monoclonal antibody.

18. The pharmaceutical composition of claim 17 wherein the antibody is a chimeric, humanized or human antibody.

19. The pharmaceutical composition of claim 18 wherein the antibody is a bispecific, multispecific or cross-reactive antibody.

20. The use of an IL-17A and/or IL-17F antagonist in the preparation of a medicament for the treatment of an insulin-resistant disorder.

21. A kit for treating an insulin-resistant disorder, said kit comprising: (a) a container comprising an IL-17A and/or IL-17F antagonist; and (b) a label or instructions for administering said antibody to treat said disorder.