



(51) International Patent Classification:

A61K 39/395 (2006.01) C07K 16/24 (2006.01)
A61P 1/16 (2006.01)

(21) International Application Number:

PCT/IL2017/050637

(22) International Filing Date:

06 June 2017 (06.06.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/345,893 06 June 2016 (06.06.2016) US

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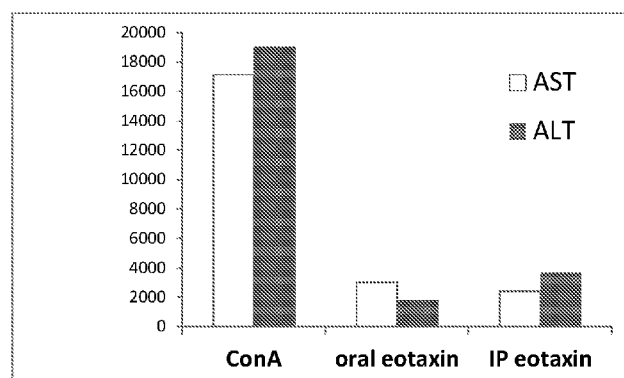
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: ANTI-EOTAXIN FOR IMMUNOPROTECTION AND HEPATOPROTECTION



	ConA, oral	ConA, IP	oral, IP
ALT	0.000000009	0.00000003	0.00099
AST	0.00006	0.00000003	0.35466

FIGURE 1

(57) Abstract: The present invention relates to compositions and methods using oral, intra rectal, intra nasal, or intradermal administration of anti-eotaxin-1 for controlling altered insulin resistance and/or hepatic function in a subject, treating an immune related disorder, treating liver damage and restoring liver function, treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug, and for enhancing the therapeutic effect of a therapeutic agent in a subject.



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

ANTI-EOTAXIN FOR IMMUNOPROTECTION AND HEPATOPROTECTION**FIELD OF INVENTION**

[001] The present invention relates to combined therapeutic compositions with a capability
5 to control the immune system. Compositions of the present invention are particularly
applicable to a range of hepatic disorders, including fatty liver disease and various types of
hepatitis, as well as to metabolic disorders such as diabetes and related conditions, and
further to various inflammatory disorders, immune-mediated and immune associated
disorders, and malignancies.

BACKGROUND OF THE INVENTION

[002] Personalized therapies are designed to optimize safety-to-efficacy ratio by selecting
patients with higher response rates based on specific biomarkers. Eotaxin-1 is an eosinophil
specific chemokine which plays a role in both innate and adaptive immune responses.
Eotaxin-1 modulates the cross talk between key cells involved in inflammation.
15 Bertilimumab is a novel first-in-class monoclonal antibody that blocks eotaxin-1. It is
designed for personalized therapy in patients with high eotaxin-1 levels -mediated
inflammatory conditions.

[003] High eotaxin-1 levels were described in patients with NonAlcoholic Fatty Liver
Disease (NAFLD), NonAlcoholic SteatoHepatitis (NASH), insulin resistance, diabetes, and
20 primary sclerosing cholangitis.

[004] Alleviation of insulin resistance is associated with decreased eotaxin-1 levels.
Parenteral administration of Bertilimumab is currently in clinical development in patients
with high eotaxin-1 levels suffering from bullous pemphigoid, inflammatory bowel disease,
or atopic dermatitis.

25 [005] Eotaxin-1 is ubiquitous throughout the normal gastrointestinal tract; however, the
potential role of gut eotaxin-1 in systemic immune functions was not previously described.
The present invention is based on a novel and unexpected finding of a biological activity and
immunomodulatory effect of oral administration of anti-eotaxin-1 antibody.

Nonalcoholic fatty liver disease (NAFLD)

[006] NAFLD is rapidly becoming a worldwide public health problem. It is the most common liver disease in the US and, indeed, worldwide. Current estimates are that ~20% of the general US population has NAFLD. The prevalence in the morbidly obese population has been estimated as 75–92%, while that in the pediatric population as 13–14%. At present, it is estimated that ~6 million individuals in the US general population have progressed to nonalcoholic steatohepatitis (NASH) and ~600,000 to NAFLD-related cirrhosis. Thus, the number of individuals at risk for end-stage liver disease and development of primary liver cancer and those potentially eligible for liver transplant is large. The prevalence of NAFLD appears to be increasing, in part due to the increasing numbers of adult and pediatric individuals who are either obese or overweight, have metabolic syndrome or type-2 diabetes, all major risk factors for development of NAFLD. Thus, there is a major need for therapeutic compounds, food supplements, food additives, medical foods, botanical drugs and safe drugs assisting in control of blood sugar levels and thereby facilitating prevention and amelioration of related disorders.

SUMMARY OF THE INVENTION

[007] A first aspect of the invention relates to compositions for controlling altered insulin resistance and/or accumulation of fat, and/or hepatic function, treating various metabolic and immunological conditions, including diabetes and inflammatory disorders, and further treating various related malignancies, and still further treating liver damage and restoring liver function, and treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug, and enhancing the therapeutic effect of a therapeutic agent. More specifically, the compositions of the invention may comprise as an active ingredient an anti-eotaxin-1 antibody.

BRIEF DESCRIPTION OF THE DRAWINGS

[008] The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features, and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanying drawings in which:

[0009] **Figure 1** shows the effect of oral and IP administration of anti-eotaxin on serum alanine transaminase (ALT) and aspartate aminotransferase (AST) liver enzymes. Male C57Bl/6 mice (11–12 weeks old) were tested for ALT and AST 24 hours after Concanavalin A (Con A) treatment (500 µg/mouse). Anti-eotaxin, when administered, was administered at 200 ng/mouse OP or IP 2 hours prior to Con A treatment. Statistically significant effects of both oral and IP anti-eotaxin administration on AST and ALT levels after ConA administration are reported in the table.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

[0010] Eotaxin 1 plays a role in various immune scenarios, and high eotaxin 1 levels were noted in several immune-mediated disorders. High serum eotaxin 1 levels were described in patients with diabetes, obesity, colitis and other disorders. Weight loss was described to be associated with reduction of eotaxin 1 levels and with improved glucose control.

[0011] Parenteral administration of anti-eotaxin-1 antibodies was shown to alleviate immune-mediated disorders. However, **oral or intrarectal or intranasal or intradermal administration** was not previously described to exert an immune modulatory effect. Thus, the present invention provides compositions for use in at least one of, a method for controlling altered insulin resistance and/or hepatic function in a subject, a method for the treatment of an immune related disorder, a method of treating liver damage, reducing liver steatosis, and restoring liver function, a method for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug, and a method for enhancing and augmenting the therapeutic effect of a therapeutic agent in a subject treated with said agent using **non-parenteral administration of anti-eotaxin-1**.

[0012] In specific embodiments, an immune-related disorder that is treated by compositions and methods of the invention may be any one of an inflammatory disorder, an autoimmune disorder, an infectious disease and a proliferative disorder.

[0013] It is further conceived that for the purpose of specific embodiments and methods, the combined composition of the invention may be an add-on to any type of drugs or therapeutic compounds administered orally, intravenously, intradermally, by inhalation or intrarectally. Examples of such combined compositions include, but are not limited to a tissue derived antigens, tumor associated antigens, or viral and or bacterial and or fungal and or parasitic

or bacterial derived antigens, or any type of organism derived antigens. It should be further noted that the compositions of the invention may be add-on to any type of healthy or diseased tissue derived antigens, or any type of drug or therapeutic compound, or any type of organism derived antigens, or hormones, or cytokines, or antibody, or any type of natural or non-natural compound that may have therapeutic properties. More specifically, such add-on preparation may be used for promoting the effect of said therapeutic compound, for exerting an adjuvant effect, or for improving the therapeutic effect of said drug, compound, or antigen.

[0014] Of particular relevance to this context, compositions of the invention as add-on products to hormones, including but not limited to insulin, whether natural or synthetic as well as any other or procedure used for the treatment of obesity, diabetes, and fatty liver disease.

[0015] It is further contemplated that a composition of the present invention is used in a method for treating liver damage, fat accumulation, and/or restoring liver function in a subject in need thereof, said composition comprising a therapeutically effective amount of anti-eotaxin-1.

[0016] Specific embodiments of the above application may include disorders wherein said subject is suffering from a liver disease, said liver disease is any one of viral, bacterial, fungal or parasitic liver disease, alcoholic or autoimmune hepatitis, alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, non-alcoholic fatty liver disease (NAFLD), liver steatosis, alcoholic or nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, drug-induced liver disease and pediatric liver disease and metabolic liver disease.

[0017] In further specific embodiments, a composition of the invention is used in a method for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug and for restoring liver function.

[0018] Of particular relevance are drugs from the group of analgesics or antipyretics that have been related to adverse effects in the liver or other forms of liver damage.

[0019] The tissue-damaging effects of hyperglycemia are well known in diabetic patients, including microvascular complications (retinopathy and nephropathy), macrovascular complications (ischemic heart disease, vascular disease, stroke and renal artery stenosis)

and neuropathies. Microvascular tissue damage is the results of hyperglycaemia per se. Macrovascular complications are found to be associated with insulin-resistant states and hyperinsulinaemia. Due to these complications, diabetes is also a most frequent cause of blindness and cardiovascular disease. Certain cells types are known to be vulnerable to direct
5 damage from chronic hyperglycemia, for e.g. mesangial cells of kidney, vascular endothelial cells, pancreatic beta cells, Schwann cells and neurons.

[0020] Alcohol affects virtually every organ and tissue in the body, with multi-factorial actions on cellular and molecular functions. Alcohol itself alters biological function by direct interaction with cellular components and also due to the effect of alcohol metabolism on the
10 systemic oxidative and inflammatory state. Alcohol metabolism produces acetaldehyde and reactive oxygen (and other) species, biochemical moieties that damage healthy tissue. Oxidative stress ensuing from these reactive oxygen and nitrogen species in many organs and tissues may vary in severity depending on the systemic inflammatory and oxidative state, and on systemic and local immune function.

15 [0021] In specific embodiments, compositions of the present invention are particularly applicable to prevent liver and/or pancreatic tissue damage. Hazardous effects of alcohol on progressive and irreversible damage of the pancreatic (chronic pancreatitis) and liver (liver cirrhosis) tissues are well documented. There is an increased incidence of cirrhosis in diabetic patients, 80% of which have glucose intolerance.

20 [0022] Further, obstruction of pancreatic and liver damage by compositions of the present invention is particularly important for maintenance of glucose homeostasis, the liver being the major organ for insulin-mediated glycogen storage and the pancreas – for production of insulin and glucagon. In this sense, compositions of the present invention are intended to prevent any condition associated with alteration of pancreatic or liver function or alteration
25 of pancreatic or liver metabolic capacity. Those conditions may include drug-induced pancreatic and liver damage, inflammatory pancreatic and liver damage resulting from infections and autoimmune disorders, pancreatic and liver malignancies and other pancreatic and liver dysfunctions.

[0023] Still further, compositions of the present invention may be used for prevention of
30 any target organ damage related to conditions associated with abnormal glucose homeostasis, such as hepatic disorders, pancreatic dysfunction, diabetes, obesity, insulin

resistance, metabolic disorders or any type of inflammation of the pancreas, liver, muscle or the adipose tissue.

[0024] It is another important aspect of the present invention to provide a method for controlling altered insulin resistance and/or hepatic function, and treating an immune related disorder, treating liver damage, restoring liver function and for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug on an organ or tissue.

[0025] Compositions of the invention can be incorporated into a pharmaceutical composition suitable for oral or mucosal administration, e.g., by ingestion, inhalation, or absorption, e. g., via nasal, intranasal, pulmonary, buccal, sublingual, rectal, dermal, or vaginal administration. Such compositions can include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active antibody compounds can be incorporated with recipients and used in solid or liquid (including gel) form. Oral compositions can also be prepared using an excipient. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. Oral dosage forms comprising the above described combinations are provided, wherein the dosage forms, upon oral administration, provide a therapeutically effective blood level of the combined compositions to a subject. Also provided are mucosal dosage forms comprising said combinations wherein the dosage forms, upon mucosal administration, provide a therapeutically effective blood level of the combined compositions to a subject. For the purpose of mucosal therapeutic administration, the active combined compounds can be incorporated with excipients or carriers suitable for administration by inhalation or absorption, e.g., via nasal sprays or drops, or rectal or vaginal suppositories.

[0026] The dosage forms of the present invention can be unit dosage forms wherein the dosage form is intended to deliver one therapeutic dose per administration, e.g., one tablet is equal to one dose. Such dosage forms can be prepared by methods of pharmacy well known to those skilled in the art. Typical oral dosage forms can be prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets)

include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents. Examples of excipients suitable for use in oral liquid dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Tablets and capsules
5 represent convenient pharmaceutical compositions and oral dosage forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or non-aqueous techniques. Such dosage forms can be prepared by any of the pharmaceutical methods known in the art. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers,
10 finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[0027] Although preferred administration is oral or mucosal, it should be appreciated that compositions of the invention may be also suitable for intravenous, intramuscular, subcutaneous, intraperitoneal, transdermal, sublingual, topical administration, or any
15 combination thereof.

[0028] It is thus conceived that the above pharmaceutical compositions, in their various formulations, are particularly applicable to treatment of certain clinical disorders, including a hepatic disorder, pancreatic dysfunction, diabetes, obesity, insulin resistance, metabolic syndrome, alcohol intoxication, alcohol withdrawal and vertigo, an inflammation of
20 pancreas, liver, muscle or the adipose tissue, and conditions related thereto.

[0029] In specific embodiments, therapeutic applications of pharmaceutical compositions of the invention include an inflammatory disorder, an autoimmune disorder, an infectious disease and a proliferative disorder.

[0030] Further, it is conceived that for the purpose of specific therapeutic applications,
25 pharmaceutical compositions of the present invention further comprise at least one additional therapeutic agent which is aimed to target the same disorder thus providing an additive or a synergistic effect between the non-parenteral administered anti-eotaxin 1 antibody and the additional drug.

[0031] Still further, in certain embodiments, the additional therapeutic agent may be an
30 immuno-modulatory antibody being administered orally, intrarectally, by inhalation or

intradermally. Such antibodies may include, but are not limited to, anti-eotaxin-1 or any type of eotaxins.

[0032] In one embodiment, the anti-eotaxin-1 antibody used in any of the methods, compositions, or kits of the present invention comprises CAT-213 or CAT-212. CAT-212
5 and CAT-213 are described and may be prepared as described in WO/2001/066754, which is incorporated herein by reference.

[0033] These antibodies may be combined with the combined composition of the invention and/or with any of the above compounds for prevention or amelioration of toxicity or unwanted side effects of sugar, alcohol or any drug. Alternatively, these antibodies may be
10 combined with the compositions of the invention and/or any of the compounds described above for augmenting the beneficial effects of these antibodies or of any of the compounds described herein above.

[0034] More specifically, said compositions are applicable to liver diseases which is any one of viral, bacterial, fungal or parasitic liver disease, alcoholic or autoimmune hepatitis,
15 alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, non-alcoholic fatty liver disease (NAFLD), liver steatosis, alcoholic or nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, drug-induced liver disease and pediatric liver disease and metabolic liver disease.

[0035] Thus, in yet another embodiment the acute or chronic toxic effect of acetaminophen
20 treated by the combined composition of the invention may be any one of drug induced liver injury (DILI), drug-induced acute steatosis, cytotoxic hepatocellular injury, acute liver failure (ALF), reperfusion injury, ischemic liver disease and acute cholestatic injury.

[0036] According to one specific embodiment, the pharmaceutical combined composition of the invention is particularly applicable for treating, preventing, ameliorating, reducing or
25 delaying the onset of drug induced liver injury (DILI), caused by acetaminophen.

[0037] In specific embodiments, therapeutic methods of the invention are implemented for the prevention or alleviation of symptoms related to a condition associated with altered insulin resistance and/or hepatic function, wherein said condition is any one of pre-diabetes, diabetes, obesity, hepatic disorder, pancreatic dysfunction, weight gain, alcohol intoxication,

alcohol withdrawal and vertigo, any condition associated with alteration of pancreatic or liver function or tissue or organ damage, and drug-induced hepatic dysfunction.

[0038] In further specific embodiments, therapeutic methods of the invention are implemented for treating a subject suffering from a disorder associated with altered insulin
5 resistance and/or hepatic function.

[0039] In other specific embodiments, therapeutic methods of the invention are implemented for the treatment of any one of a hepatic disorder, pancreatic dysfunction, diabetes, obesity, insulin resistance, metabolic syndrome, alcohol intoxication, alcohol withdrawal and vertigo, an inflammation of pancreas, liver, muscle or the adipose tissue,
10 inflammatory disorder and a malignancy.

[0040] Further in this connection, the terms treatment or prevention as used herein refers to the complete range of therapeutically positive effects of administering to a subject including inhibition, reduction of, alleviation of, and relief from, a condition, illness, symptoms or undesired side effects thereof. These also include treatment or prevention of recurrence of a
15 disease in response to a treatment with a non-effective, or deleterious therapeutic agent, and prevention or postponement of disease development, prevention or postponement of development of symptoms and/or a reduction in the severity of such symptoms that will or are expected to develop. These further include ameliorating existing symptoms, preventing-additional symptoms and ameliorating or preventing the underlying metabolic causes of
20 symptoms.

[0041] The term prevention is interchangeable with prophylaxis in referring to significant reduction of risk of occurrence of a biological or medical event that is sought to be prevented in a tissue, a system, animal or human by a researcher, veterinarian, medical doctor or other clinician, and the term prophylactically effective amount is intended to mean that amount of
25 a pharmaceutical composition that will achieve this goal.

[0042] Thus, it is conceived that methods using any of the above compositions of the invention are applicable for controlling blood sugar levels in a subject, treating an immune related disorder, treating liver damage, reducing fat accumulation, restoring liver function and for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic
30 toxic effect of a drug on any body organs or tissues.

[0043] Particularly for pre-clinical applications, methods of the invention use any of the above compositions in formulations adapted for add-on to a solid, semi-solid or liquid food, beverage, food additive, food supplement, medical food, botanical drug, drug and/or a pharmaceutical compound.

- 5 [0044] In specific pre-clinical applications, methods of the invention use the above compositions as add-on to foods and/or beverages comprising an increased content of sugar and/or alcohol.

[0045] Methods using the above compositions of the invention are particularly applicable for controlling blood sugar levels in a subject, wherein said control is inhibiting increase or
10 decrease in blood sugar levels, improving glucose tolerance or altering insulin resistance state.

[0046] In certain embodiments, methods of the present invention are applicable to the prevention or alleviation of symptoms related to a condition associated with increased or decreased blood sugar levels, wherein said condition is any one of a hepatic disorder,
15 pancreatic dysfunction, diabetes, obesity, weight gain, alcohol intoxication, alcohol withdrawal, vertigo, and tissue or organ damage or any condition associated with alteration of pancreatic or liver function in a way that alter insulin resistance and liver metabolic capability.

[0047] The present invention is directed at treating, controlling or preventing a number of
20 medical conditions. In general, the terms preventing, controlling and treating encompass a range of conditions, starting from prevention of the development of a disease or a symptom in a patient who may predisposed to a disease but has yet been diagnosed; further including reduction, retardation or inhibition of progression symptoms of a disease; and also alleviation of symptoms of an already existing disease, i.e. reversal of said symptoms.

- 25 [0048] Methods and compositions of the invention are specifically relevant to treating, controlling, ameliorating, or preventing body weight gain, obesity, metabolic syndrome and diabetes.

[0049] By body weight gain is meant specifically body fat gain that is maintained or decreased by applying the methods and compositions of the invention. A decrease in weight
30 or body fat may protect against cardiovascular disease by lowering blood pressure, total

cholesterol, LDL cholesterol and triglycerides, and may alleviate symptoms associated with chronic conditions such as hypertension, coronary heart disease, type 2 diabetes, osteoarthritis, sleep apnea and degenerative joint disease.

[0050] The present invention is applicable to all types of obesity, including endogenous
5 obesity, exogenous obesity, hyper-insulin obesity, hyperplastic-hypertrophic obesity, hypertrophic obesity, hypothyroid obesity and morbid obesity. Moreover, inflammation-mediated obesity may be treated particularly effectively in accordance with the invention.

[0051] By metabolic syndrome, or syndrome X, is meant a complex multi-factorial condition accompanied by an assortment of abnormalities including hypertension, hyper-
10 triglyceridemia, hyperglycemia, low high-density lipoprotein (HDL) cholesterol and abdominal obesity, which, among others, may lead to pro-thrombotic (e.g., elevated fibrinogen or plasminogen activator inhibitor-1 in the blood) and pro-inflammatory (e.g., elevated C-reactive protein (CRP) in the blood) conditions.

[0052] Each of the disorders associated with metabolic syndrome are risk factors in their
15 own right, and can promote atherosclerosis, cardiovascular disease, stroke, and other adverse health consequences. However, when present together, these factors are predictive of increased risk of cardiovascular disease and stroke.

[0053] In the context of the present invention, controlling or treating metabolic syndrome using the combined compositions of the invention, is meant reducing severity and/or number
20 of symptoms associated with this medical condition, i.e. reducing any one of elevated blood glucose, glucose intolerance, insulin resistance, elevated triglycerides, elevated LDL-cholesterol, low HDL cholesterol, elevated blood pressure, abdominal obesity, pro-inflammatory states, and pro-thrombotic states. Additionally or alternatively, it is meant reducing the risk and/or the onset of developing associated diseases, i.e. cardiovascular
25 disease, coronary heart disease and other diseases related to plaques in the artery walls and diabetic conditions.

[0054] Further, methods and compositions of the invention are particularly advantageous for treating, controlling and preventing diabetes or diabetic conditions, such as type 1 diabetes, type 2 diabetes, gestational diabetes, pre-diabetes, slow onset autoimmune diabetes
30 type 1 (LADA), hyperglycemia or any type of condition or compound that expose the patient

to pre diabetes or to diabetes or that alters the stage of insulin resistance. For the purposes of treatment, the diabetes may be overt, diagnosed diabetes, e.g., type 2 diabetes, or a pre-diabetic condition.

5 [0055] According to another embodiment, methods according to the invention may further lead to a significant reduction in pancreatic hyperplasia and hepatic fat accumulation.

[0056] Still further, according to another embodiment, methods according to the invention may alter the function of macrophages while increasing foxp3+ or any other type of regulatory T cells in fat tissue or in the body, suppresses inflammatory cytokine production by adipocytes and clearly leads to a marked decrease of inflammatory cell infiltration to fat
10 tissue of a treated subject, specifically, a subject suffering from an immune-related disorder. Eotaxin-1 is an eosinophil specific chemokine which plays a role in both innate and adaptive immune responses. Eotaxin-1 modulates the cross talk between key cells involved in inflammation. Any of these can be a direct effect on eosinophils or on any other cross talk between innate and adaptive cells, or a cross talk between eosinophil and these cells.

15 [0057] More particularly, methods of the invention are intended for treatment of dyslipoproteinemia, which may include hypertriglyceridemia, hypercholesterolemia and low HDL-cholesterol, obesity, NIDDM (non-insulin dependent diabetes mellitus), IGT (impaired glucose tolerance), blood coagulability, blood fibronolysis defects and hypertension.

20 [0058] According to some embodiments of, methods and compositions of the invention can be used to prevent, treat and control liver diseases and disorders including hepatitis, cirrhosis, non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease- (NAFLD), hepatotoxicity and chronic liver disease. In general, the terms `prevent`, `control` and `treat` encompass the prevention of the development of a disease or a symptom from a patient who
25 may have a predisposition of the disease or the symptom but has yet been diagnosed to have the disease or the symptom; the inhibition of the symptoms of a disease, namely, inhibition or retardation of the progression thereof; and the alleviation of the symptoms of a disease, namely, regression of the disease or the symptoms, or inversion of the progression of the symptoms.

[0059] For specific applications of the invention, said disorder may any one of a hepatic disorder, pancreatic dysfunction, diabetes, obesity, insulin resistance, metabolic syndrome, alcohol intoxication, alcohol withdrawal, and tissue or organ damage.

5 [0060] In specific embodiments, therapeutic methods of the invention are used for treating, preventing, ameliorating, reducing or delaying the onset of an immune-related disorder.

[0061] In more specific embodiments, said therapeutic methods are applied for any one of an inflammatory disorder, an autoimmune disorder, an infectious disease and a proliferative disorder.

10 [0062] In this context, immune-related disorder may be any one of an inflammatory disorder, an autoimmune disorder, an infectious disease and a proliferative disorder.

[0063] Immune therapy involves the exposure of components of the immune system to various elements (cytokines, disease associated antigens and natural metabolites) to combat disease processes in which a dysregulated immune response is thought to play a role. Immune dysregulation is thought to play a major part in the pathogenesis or disease course
15 of a great number of disease processes, including various neoplastic, inflammatory, autoimmune, infectious and genetic entities.

[0064] In yet other embodiments, methods of the invention may be used for the treatment of an autoimmune disorder. Examples of autoimmune disorders include, but are not limited to, Asthma, Primary sclerosing cholangitis, Alopecia Areata, Lupus, Ankylosing
20 Spondylitis, Meniere's Disease, Antiphospholipid Syndrome, Mixed Connective Tissue Disease, Autoimmune Addison's Disease, Multiple Sclerosis, Autoimmune Hemolytic Anemia, Myasthenia Gravis, Autoimmune Hepatitis, Pemphigus Vulgaris, Behcet's Disease, Pernicious Anemia, Bullous Pemphigoid, Polyarthritis Nodosa, Cardiomyopathy, Polychondritis, Celiac Sprue-Dermatitis, Polyglandular Syndromes, Chronic Fatigue
25 Syndrome (CFIDS), Polymyalgia Rheumatica, Chronic Inflammatory Demyelinating, Polymyositis and Dermatomyositis, Chronic Inflammatory Polyneuropathy, Primary Agammaglobulinemia, Churg-Strauss Syndrome, Primary Biliary Cirrhosis, Cicatricial Pemphigoid, Psoriasis, CREST Syndrome, Raynaud's Phenomenon, Cold Agglutinin Disease, Reiter's Syndrome, Crohn's Disease, Rheumatic Fever, Discoid Lupus, Rheumatoid
30 Arthritis, Essential Mixed, Cryoglobulinemia Sarcoidosis, Fibromyalgia, Scleroderma,

Grave's Disease, Sjogren's Syndrome, Guillain-Barre, Stiff- Man Syndrome, Hashimoto's Thyroiditis, Takayasu Arteritis, Idiopathic Pulmonary Fibrosis, Temporal Arteritis/Giant Cell Arteritis, Idiopathic Thrombocytopenia Purpura (ITP), Ulcerative Colitis, IgA Nephropathy, Uveitis, Insulin Dependent Diabetes (Type I), Vasculitis, Lichen Planus, and
5 Vitiligo. The oral combined SE and Cremophore EL compositions described herein can be administered to a subject to treat or prevent disorders associated with an abnormal or unwanted immune response associated with cell, tissue or organ transplantation, e.g., renal, hepatic, and cardiac transplantation, e.g., graft versus host disease (GVHD), or to prevent allograft rejection.

10 [0065] According to specific embodiments, an autoimmune disease treated by methods of the invention may be any one of rheumatoid arthritis, type 1 diabetes, type 2 diabetes, arterosclerosis, asthma, acute and chronic graft versus host disease, systemic lupus erythmatosus, scleroderma, multiple sclerosis, inflammatory bowel disease, psoriasis, uvietis, thyroiditis and immune mediated hepatitis.

15 [0066] According to other embodiments, methods of the invention are applicable to the treatment of Multiple Sclerosis (MS). MS is typically characterized clinically by recurrent or chronically progressive necrologic dysfunction, caused by lesions in the CNS. Pathologically, the lesions include multiple areas of demyelination affecting the brain, optic nerves, and spinal cord. The underlying etiology is uncertain, but MS is widely believed to
20 be at least partly an autoimmune or immune-mediated disease.

[0067] According to another preferred embodiment, methods of the invention may be used for treating any inflammatory arthritis. In specific embodiments, the compositions and methods of the invention may be applicable for treating Rheumatoid arthritis (RA). RA is the most common chronic inflammatory arthritis and affects about 1% of adults, it is two to
25 three times more prevalent in women than in men. RA may begin as early as infancy, but onset typically occurs in the fifth or sixth decade.

[0068] Methods of the invention described herein can also be used to treat or prevent graft rejection in a transplant recipient. For example, methods of the invention can be used in a wide variety of tissue and organ transplant procedures, e.g., can be used to induce central
30 tolerance in a recipient of a graft of cells, in stem cells such as bone marrow and/or of a tissue or organ such as pancreatic islets, liver, kidney, heart, lung, skin, muscle, neuronal

tissue, stomach, and intestines. Thus, the new methods can be applied in treatments of diseases or conditions that entail cell, tissue or organ transplantation (e.g. liver transplantation to treat hypercholesterolemia, transplantation of muscle cells to treat muscular dystrophy, or transplantation of neuronal tissue to treat Huntington's disease or
5 Parkinson's disease).

[0069] According to another embodiment, methods of the invention may modulate the T cells or other cells balance towards a suppressing response in a subject suffering from IBD. Therefore, according to one embodiment, the composition of the invention is intended for treating IBD. Inflammatory bowel diseases (IBD) are common gastrointestinal disorders that
10 can be perceived as being the result of a dysbalance between pro-inflammatory and anti-inflammatory subtypes of immune responses.

[0070] In yet other embodiments, methods and compositions of the invention may be used for the treatment of atherosclerosis. Atherosclerosis is a slowly progressive disease characterized by the accumulation of cholesterol within the arterial wall. The atherosclerotic
15 process begins when LDL-C becomes trapped within the vascular wall. Oxidation of the LDL-C results in the bonding of monocytes to the endothelial cells lining the vessel wall. These monocytes are activated and migrate into the endothelial space where they are transformed into macrophages, leading to further oxidation of LDL-C. The oxidized LDL-C is taken up through the scavenger receptor on the macrophage leading the formation of
20 foam cells. A fibrous cap is generated through the proliferation and migration of arterial smooth muscle cells, thus creating an atherosclerotic plaque. Lipids depositing in atherosclerotic regions are derived primarily from plasma apo B containing lipoproteins. These include chylomicrons, LDL-C, IDL, and VLDL. This accumulation forms bulky plaques that inhibit the flow of blood until a clot eventually forms, obstructing an artery and
25 causing a heart attack or stroke.

[0071] Thus, in other specific embodiments, methods and compositions of the invention are intended for the treatment of a malignancy. In cancerous situations, modulation of the T cell balance may be in the direction of inducing a pro-inflammatory response or in augmenting the anti-tumor associated antigens immunity. As used herein to describe the present
30 invention, "cancer", "tumor" and "malignancy" all relate equivalently to a hyperplasia of a tissue or organ. If the tissue is a part of the lymphatic or immune systems, malignant cells

may include non-solid tumors of circulating cells. Malignancies of other tissues or organs may produce solid tumors. In general, the compositions of the present invention may be used in the treatment of non-solid and solid tumors.

[0072] Malignancy, as contemplated in the present invention may be selected from the group consisting of carcinomas, melanomas, lymphomas, myeloma, leukemia and sarcomas. Malignancies that may find utility in the present invention can comprise but are not limited to hematological malignancies (including leukemia, lymphoma and myeloproliferative disorders), hypoplastic and aplastic anemia (both viral and or bacterial and or fungal and or parasitically induced and idiopathic), myelodysplastic syndromes, all types of paraneoplastic syndromes (both immune mediated and idiopathic) and solid tumors (including lung, liver, breast, colon, prostate GI tract, pancreas and Kaposi). More particularly, the malignant disorder may be hepatocellular carcinoma, colon cancer, melanoma, myeloma, acute or chronic leukemia.

[0073] It should be noted that the immuno-modulatory methods and compositions of the invention may be applicable for treating infectious diseases caused by bacterial infections, viral and or bacterial and or fungal and or parasitic infections, fungal infections, or parasitic infections. More specifically, the viral and or bacterial and or fungal and or parasitic infection may be caused by any one of HBV, HCV or HIV.

[0074] In more specific embodiments, such methods may be introduced to a subject that is suffering from a liver disease, said liver disease is any one of viral, bacterial, fungal or parasitic liver disease, alcoholic or autoimmune hepatitis, alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, non-alcoholic fatty liver disease (NAFLD), liver steatosis, alcoholic or nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, drug-induced liver disease and pediatric liver disease and metabolic liver disease.

[0075] In yet other specific embodiments, therapeutic methods of the invention may be implemented for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug and for restoring liver function.

[0076] In more specific embodiments, therapeutic methods of the invention may be applied as above to prevent, ameliorate, or reduce effects of a drug that is an analgesic or an antipyretic drug, and restore liver function.

[0077] More specifically, the present methods may apply to a subject suffering from a liver disease, that may be any one of viral and or bacterial and or fungal and or parasitic, alcoholic or autoimmune hepatitis, alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, non-alcoholic fatty liver disease (NAFLD), any type of liver steatosis, for example, due to
5 other disease such as Wilson's disease or alpha 1 anti-trypsin deficiency, alcoholic or nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, drug-induced liver disease and pediatric liver disease and any type of metabolic liver disease, for example, glycogen storage disease

[0078] In some embodiments, methods of the invention may further comprise concurrent or
10 parallel administration of at least one additional therapeutic agent.

[0079] More specifically, such methods are applicable for treating subjects suffering for example from a liver disease, said liver disease is any one of viral, bacterial, fungal or parasitic liver disease, alcoholic or autoimmune hepatitis, alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, non-alcoholic fatty liver disease (NAFLD), liver steatosis,
15 alcoholic or nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, drug-induced liver disease and pediatric liver disease and any type metabolic liver disease, for example glycogen storage disease.

[0080] Specific embodiments of said methods are applicable for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug and
20 for restoring liver function.

[0081] One clinically important type of liver disease is hepatitis. Hepatitis is an inflammation of the liver that can be caused by viruses (e.g., hepatitis virus A, B and C (HAV, HBV, and HCV, respectively), chemicals, drugs, alcohol, inherited diseases, or the patient's own immune system (autoimmune hepatitis). This inflammation can be acute and
25 resolve within a few weeks to months, or chronic, and persist over many years. Chronic hepatitis can persist for decades before causing significant symptoms, such as cirrhosis (scarring and loss of function), liver cancer, or death. Other important examples of the different diseases and disorders encompassed by the term "liver disease" and suitable for treatment or prevention or control using the compositions and methods of the present
30 invention include, but are not limited to amebic liver abscess, biliary atresia, fibrosis, cirrhosis, coccidioidomycosis, delta agent, hepatocellular carcinoma (HCC), alcoholic liver

disease, primary biliary cirrhosis, pyogenic liver abscess, Reye's syndrome, sclerosing cholangitis, and Wilson's disease. In some embodiments, the compositions and methods described herein are suitable for the treatment of liver disease characterized by the loss or damage of parenchymal liver cells. In some aspects, the etiology of this can be a local or systemic inflammatory response. As the ConA immune mediated hepatitis model, the beneficial effect of SE in this model forms the basis for its potential beneficial effect in any immune-related disease, in which the immune system plays a role in the pathogenesis thereof. Such immune-related diseases include infectious, inflammatory, and malignant disorders.

[0082] Chronic liver failure occurs over months to years and is most commonly caused by viruses (e.g., HBV and HCV), long-term/excessive alcohol consumption, cirrhosis, hemochromatosis, and malnutrition. Acute liver failure is the appearance of severe complications after the first signs of liver disease (e.g., jaundice) and includes a number of conditions, all of which involve severe hepatocyte injury or necrosis. In some embodiments, the compositions and methods described herein are particularly suitable for the treatment of hyperacute, acute, and subacute liver failure, fulminant hepatic failure and late onset fulminant hepatic failure, all of which are referred to herein as "acute liver failure." Common causes for acute liver failure include, for example, viral and or bacterial and or fungal and or parasitic hepatitis, exposure to certain drugs and toxins (e.g., fluorinated hydrocarbons (e.g., trichloroethylene and tetrachloroethane), amanita phalloides (e.g., commonly found in the "death-cap mushroom"), acetaminophen (paracetamol), halothanes, sulfonamides, henytoins), cardiac-related hepatic ischemia (e.g., myocardial infarction, cardiac arrest, cardiomyopathy, and pulmonary embolism), renal failure, occlusion of hepatic venous outflow (e.g., Budd-Chiari syndrome), Wilson's disease, acute fatty liver of pregnancy, amebic abscesses, and disseminated tuberculosis.

[0083] Non-alcoholic steatohepatitis or NASH is a condition of the liver in which inflammation is caused by a buildup of fat in the liver. NASH is part of a group of liver diseases, known as nonalcoholic fatty liver disease, in which fat builds up in the liver and sometimes causes liver damage that gets worse over time (progressive liver damage). "Non-alcoholic fatty liver disease" (NAFLD) is fatty inflammation of the liver which is not due to excessive alcohol use. It is related to insulin resistance and the metabolic syndrome, obesity,

high cholesterol and triglycerides, and diabetes and may respond to treatments originally developed for other insulin resistant states (e.g. diabetes mellitus type 2), such as weight loss, metformin and thiazolidinediones. Non-alcoholic steatohepatitis (NASH) is the most extreme form of NAFLD, which is regarded as a major cause of cirrhosis of the liver of
5 unknown cause.

[0084] Other factors that have been known to contribute to NASH include: surgery that shorten the intestines, the stomach, or both, such as jejunal bypass operation or biliopancreatic diversion; prolonged use of feeding tube or other method of receiving nutrition; certain drugs, including amiodarone, glucocorticoids, synthetic estrogens, and
10 tamoxifen.

[0085] NASH is a condition that may get worse over time (called a progressive condition) and can cause scarring (fibrosis) of the liver, which leads to cirrhosis. "Cirrhosis" describes a condition in which liver cells have been replaced by scar tissue. The term "cirrhosis of the liver" or "cirrhosis" is used to describe a chronic liver disease characterized by replacement
15 of liver tissue by fibrous scar tissue as well as regenerative nodules, leading to progressive loss of liver function. Cirrhosis is most commonly caused by fatty liver disease, including NASH, as well as alcoholism and hepatitis B and C, but also may be of unknown cause. Potentially life-threatening complications of cirrhosis are hepatic encephalopathy (confusion and coma) and bleeding from esophageal varices. Cirrhosis has historically been thought to
20 be generally irreversible once it occurs, and historical treatment focused on preventing progression and complications. In advanced stages of cirrhosis, the only option is a liver transplant.

[0086] Each of the compounds above, specifically in the combined compositions and methods of the present invention can be used to treat, prevent or control chemical liver
25 trauma and hepatotoxicity. Also chemical trauma or acute chemical trauma to the liver refers to serious injury which occurs to a patient over a short duration as a consequence of chemical toxicity, including drug-induced toxicity or trauma. Drug-induced acute liver trauma, including acetaminophen-induced acute liver trauma, is acute liver injury which occurs as a result or consequence of exposure to a drug (e.g., drug overdose), especially acetaminophen
30 toxicity. Compounds according to the present invention are useful for reducing the injury to

the liver which occurs from physical and chemical trauma, especially including drug-induced (drug overdose) and acetaminophen-induced acute liver trauma.

[0087] Hepatotoxicity is chemical liver trauma resulting from a hepatotoxic agent, or hepatotoxicity-inducing bioactive agent. The terms "hepatotoxic agent" and "a
5 hepatotoxicity inducing bioactive agent" are used synonymously in context to describe compounds which often produce hepatotoxicity in patients administered such agents. Examples of hepatotoxicity agents include, for example, anaesthetic agents, antiviral and or bacterial and or fungal and or parasitic agents, anti-retroviral and or bacterial and or fungal and or parasitic agents (nucleoside reverse transcriptase inhibitors and non-nucleoside
10 reverse transcriptase inhibitors), especially anti-HIV agents, anticancer agents, organ transplant drugs (cyclosporin, tacrolimus, OKT3), antimicrobial agents (anti-TB, anti-fungal, antibiotics), anti-diabetes drugs, vitamin A derivatives, steroidal agents, especially including oral contraceptives, anabolic steroids, androgens, non-steroidal anti-inflammatory agents, anti-depressants (especially tricyclic antidepressants) glucocorticoids, natural
15 products and herbal and alternative remedies, especially including St. John's wort.

[0088] Hepatotoxicity may manifest as triglyceride accumulation which leads to either small droplet (microvesicular) or large droplet (macrovesicular) fatty liver. There is a separate type of steatosis where phospholipid accumulation leads to a pattern similar to the diseases with inherited phospholipid metabolism defects (e.g. Tay-Sachs disease).

20 [0089] It must be understood that the combined compositions and methods of the invention are particularly applicable for treating any of the hepatic disorders described herein above.

[0090] In certain embodiments, the method of the invention may optionally further comprises the concurrent or parallel administration of at least one additional therapeutic agent.

25 [0091] As previously mentioned, in alternative embodiments, the methods of the invention may be applicable for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug. In specific embodiments, such drug may be an analgesic or an antipyretic drug.

[0092] It should be appreciated that the composition of the invention may be used for treating, preventing and protecting from any damage caused by a therapeutic compound to any tissue or organ, and for restoring the biological function of said damaged tissue or organ.

[0093] Thus, in one embodiment, the present invention provides a method for treating, improving, or suppressing insulin resistance in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject. In one embodiment, said method comprises altering the insulin resistance state in said subject.

[0094] In another embodiment, the present invention provides a method for controlling blood sugar levels in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject. In one embodiment, the method for controlling blood sugar levels comprises inhibiting an increase in blood sugar levels. In another embodiment, the method for controlling blood sugar levels comprises decreasing blood sugar levels. In another embodiment, the method for controlling blood sugar levels comprises inhibiting an increase in blood sugar levels.

[0095] In another embodiment, the present invention provides a method for improving glucose tolerance in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.

[0096] In another embodiment, the present invention provides a method for improving or restoring hepatic function or liver function in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.

[0097] In another embodiment, the present invention provides a method for reducing accumulation of fat in the liver in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.

[0098] In another embodiment, the present invention provides a method for treating, improving, or suppressing liver damage in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.

[0099] In another embodiment, the present invention provides a method for treating, improving, or suppressing steatosis in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.

[00100] In one embodiment, said subject is suffering from a liver disease. In one embodiment, the liver disease comprises viral, bacterial, fungal or parasitic liver disease, alcoholic or autoimmune hepatitis, alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, alcoholic steatohepatitis (ASH), hepatocellular carcinoma, drug-induced liver disease, pediatric liver disease, metabolic liver disease, or a combination thereof. In another embodiment, the liver disease comprises non-alcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or a combination thereof. In one embodiment, the subject has a condition comprising pre-diabetes, diabetes, obesity, hepatic disorder, pancreatic dysfunction, weight gain, alcohol intoxication, alcohol withdrawal, a condition associated with alteration of pancreatic or liver function, a condition associated with tissue or organ damage, drug-induced hepatic dysfunction, or a combination thereof.

[00101] In another embodiment, the present invention provides a method for treating, preventing, ameliorating, reducing or delaying the onset of, improving, or suppressing an immune-related disorder in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject. In one embodiment, the immune-related disorder comprises an inflammatory disorder, an autoimmune disorder, an infection, a proliferative disorder, or a combination thereof.

[00102] In another embodiment, the present invention provides a method for reducing inflammation in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.

[00103] In another embodiment, the present invention provides a method for treating, improving, suppressing, preventing, ameliorating, reducing or delaying the onset of a toxic effect of a drug or compound in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject. In one embodiment, the toxic effect is short-term. In another embodiment, the toxic effect is long-term.

[00104] In another embodiment, the present invention provides a method for enhancing or augmenting the therapeutic effect of a therapeutic agent in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.

[00105] In one embodiment, the inhibitor of eotaxin as described in the compositions and methods of the present invention is an anti-eotaxin antibody. In one embodiment, the anti-eotaxin antibody is an anti-eotaxin-1 antibody.

[00106] In one embodiment, the composition is administered nonparenterally.

5 [00107] In one embodiment, the composition is administered orally, intranasally, intrarectally, or intradermally.

[00108] In one embodiment, treating as described herein comprises preventing or alleviating symptoms related to the condition.

[00109] In another embodiment, the present invention provides a method for treating a
10 subject suffering from a disorder associated with altered insulin resistance and/or hepatic function comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.

[00110] In one embodiment, the disorder comprises a hepatic disorder, pancreatic dysfunction, diabetes, obesity, insulin resistance, metabolic syndrome, alcohol intoxication,
15 alcohol withdrawal, vertigo, an inflammation of pancreas, liver, muscle or the adipose tissue, inflammatory disorder, a malignancy, or a combination thereof.

[00111] In another embodiment, the present invention provides a method for treating, preventing, ameliorating, reducing or delaying the onset of a neurological disorder in a subject comprising the step of administering a composition comprising an inhibitor of anti-
20 eotaxin-1 to said subject. In one embodiment, the neurological disorder comprises Alzheimer's Disease.

[00112] In one embodiment, any of the methods described herein further comprises the step of administering an additional therapeutic agent. In one embodiment, the therapeutic agent is a treatment for NASH, diabetes, obesity, an immune-associated disease, or a
25 combination thereof.

[00113] In one embodiment, a subject as described herein has high levels of eotaxin-1 in serum. In another embodiment, the subject as described herein has high levels of eotaxin-1 in a tissue.

[00114] In another embodiment, the present invention provides a kit comprising a composition comprising an inhibitor of anti-eotaxin-1 and instructions for use in any one of the methods described herein. In another embodiment, the present invention provides a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use in any one of the methods described herein.

[00115] In another embodiment, the present invention provides a composition comprising an inhibitor of anti-eotaxin-1 for controlling altered insulin resistance and/or hepatic function in a subject, for the treatment of an immune related disorder, for treating liver damage, reducing steatosis, and restoring liver function, for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug, for enhancing and augmenting the therapeutic effect of a therapeutic agent in a subject, or a combination thereof.

[00116] In one embodiment, the composition is administered nonparenterally. In one embodiment, the composition is administered orally, intranasally, intrarectally, or intradermally.

[00117] In one embodiment, the composition as described herein may be used in a method for controlling blood sugar levels in a subject. In one embodiment, the composition as described herein may be used in a method for inhibiting an increase or decrease in blood sugar levels, improving glucose tolerance or altering insulin resistance state.

[00118] In one embodiment, the composition as described herein may be used in a method for altering insulin resistance and/or hepatic function. In another embodiment, the composition as described herein may be used in a method for reducing accumulation of fat in the liver. In another embodiment, the composition as described herein may be used to reduce inflammation, which in one embodiment, is hepatic inflammation.

[00119] In one embodiment, the composition as described herein may be used for the prevention or alleviation of symptoms related to a condition associated with altered insulin resistance state and/or hepatic function. In one embodiment, the condition comprises prediabetes, diabetes, obesity, hepatic disorder, pancreatic dysfunction, weight gain, alcohol intoxication, alcohol withdrawal, any condition associated with alteration of pancreatic or liver function or tissue or organ damage, or drug-induced hepatic dysfunction.

[00120] In one embodiment, the composition as described herein may be used in a method for treating a subject suffering from a disorder associated with altered insulin resistance and/or hepatic function.

5 [00121] In one embodiment, the disorder comprises a hepatic disorder, pancreatic dysfunction, diabetes, obesity, insulin resistance, metabolic syndrome, alcohol intoxication, alcohol withdrawal and vertigo, an inflammation of pancreas, liver, muscle or the adipose tissue, inflammatory disorder and a malignancy.

[00122] In one embodiment, the composition as described herein may be used in a method for treating, preventing, ameliorating, reducing or delaying the onset of an immune-related
10 disorder, said composition comprising a therapeutically effective amount of anti-eotaxin-1.

[00123] In one embodiment, the immune-related disorder comprises an inflammatory disorder, an autoimmune disorder, an infectious disease or a proliferative disorder.

[00124] In one embodiment, the composition further comprises at least one additional therapeutic agent.

15 [00125] In one embodiment, the subject as described herein is suffering from a liver disease. In one embodiment, said liver disease comprises a viral, bacterial, fungal or parasitic liver disease. In another embodiment, said liver disease comprises alcoholic or autoimmune hepatitis, alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, nonalcoholic fatty liver disease (NAFLD), liver steatosis, alcoholic or nonalcoholic steatohepatitis (NASH),
20 hepatocellular carcinoma, drug-induced liver disease and pediatric liver disease and metabolic liver disease.

[00126] In one embodiment, the composition as described herein may be used in a method for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug, for restoring liver function, or a combination thereof.

25 [00127] In another embodiment, the present invention provides a method for controlling altered insulin resistance and/or hepatic function, and treating an immune related disorder, treating liver damage, restoring liver function and for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug on an organ or tissue, said method comprises providing to a subject at least one of an anti-eotaxin-1 antibody to
30 said subject.

[00128] In one embodiment, the present invention provides a method for controlling altered insulin resistance and/or hepatic function.

[00129] In one embodiment, the present invention provides a method for the prevention or alleviation of symptoms related to a condition associated with altered insulin resistance and/or hepatic function. In one embodiment, the condition comprises prediabetes, diabetes, obesity, hepatic disorder, pancreatic dysfunction, weight gain, alcohol intoxication, alcohol withdrawal, any condition associated with alteration of pancreatic or liver function or tissue or organ damage, drug-induced hepatic dysfunction, or a combination thereof.

[00130] In one embodiment, a disorder as described herein comprises a hepatic disorder, pancreatic dysfunction, diabetes, obesity, insulin resistance, metabolic syndrome, alcohol intoxication, alcohol withdrawal and vertigo, an inflammation of pancreas, liver, muscle or the adipose tissue, inflammatory disorder, a malignancy, or a combination thereof.

[00131] In one embodiment, the present invention provides a method for treating, preventing, ameliorating, reducing or delaying the onset of an immune-related disorder, or neurological disorder including Alzheimer disease.

[00132] In one embodiment, the immune-related disorder comprises an inflammatory disorder, an autoimmune disorder, an infectious disease, a proliferative disorder, or a combination thereof.

[00133] In one embodiment, the method further comprises the concurrent or parallel administration of at least one additional therapeutic agent.

[00134] In one embodiment, the subject is suffering from a liver disease. In one embodiment, the liver disease comprises a viral, bacterial, fungal or parasitic liver disease. In another embodiment, the liver disease comprises alcoholic or autoimmune hepatitis, alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, nonalcoholic fatty liver disease (NAFLD), liver steatosis, alcoholic or nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, drug-induced liver disease, pediatric liver disease, metabolic liver disease, or a combination thereof.

[00135] In one embodiment, the present invention provides a method for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic toxic effect of a drug and for restoring liver function.

[00136] In one embodiment, the anti-eotaxin-1 antibody in the compositions and for uses as described herein is combined with a treatment for NASH, diabetes, obesity, or any type of immune-associated disease.

[00137] In another embodiment, the present invention provides a method for treating, preventing, ameliorating, reducing or delaying the onset of acute or chronic disease in patients that have high levels of eotaxin-1 in serum or in a tissue.

[00138] In another embodiment, the present invention provides a method for lowering the level of one or more liver enzymes by administration of an inhibitor of eotaxin. In another embodiment, the present invention provides a method for suppressing an increase in the level of one or more liver enzymes resulting from a liver disorder or condition, by administration of an inhibitor of eotaxin.

[00139] In one embodiment, the liver enzyme comprises alanine transaminase (ALT). In another embodiment, the liver enzyme comprises aspartate aminotransferase (AST). In one embodiment, administration of the eotaxin inhibitor is via oral administration. In another embodiment, administration of the eotaxin inhibitor is via intraperitoneal (IP) administration. In one embodiment, the liver enzyme level is measured in the liver. In another embodiment, the liver enzyme level is measured in the serum.

[00140] In another embodiment, the present invention provides a method for treating, inhibiting or suppressing an immune-mediated hepatitis. In another embodiment, the present invention provides a method for treating, inhibiting or suppressing autoimmune hepatitis, or lupoid hepatitis.

[00141] In one embodiment, the inhibitor of eotaxin-1 is an anti-eotaxin antibody. In one embodiment, the inhibitor of eotaxin-1 is an anti-eotaxin-1 antibody. In one embodiment, the inhibitor of eotaxin-1 is Bertilimumab. In one embodiment, a therapeutically effective amount of anti-eotaxin-1 is administered.

[00142] An amount adequate to accomplish this is defined as a "therapeutically effective dose." Amounts effective for this use will depend upon the severity of the condition and the general state of the patient's own immune system, but generally range from about 0.00001 to about 1000 mg/Kg body weight. Further including dosages from 0.0001 to 5000 mg and 0.01 to 2.5, specifically, 0.001, 0.002, 0.003, 0.004, 0.005, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06,

0.07, 0.08, 0.09, 0.1, 0.2, 0.3 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5 and 5 mg of a combined composition. Single or multiple administrations on a daily, weekly or monthly schedule can be carried out with dose levels and pattern being selected by the treating physician.

5 [00143] As discussed above, the invention provides different methods of treating, ameliorating preventing or delaying the onset of hepatic or any immune-related disorders in a subject in need. As used herein in the specification and in the claims section below, the term "treat" or "treating" and their derivatives includes substantially inhibiting, slowing or reversing the progression of a condition, substantially ameliorating symptoms of a condition
10 or substantially preventing the appearance of symptoms of a condition, said condition is any one of an immune-related disorder and a hepatic disorder in a subject in need thereof.

[00144] The term "prevent" and all variations of this term is intended to mean the countering in advance of pathologic symptoms or a pathologic process progress. In this case it is understood that the composition is applied prior to the observation of clinical symptoms.

15 [00145] The terms "ameliorate" and "amelioration" relate to the improvement in the treated subject condition brought about by the compositions and methods according to the invention, wherein said improvement may be manifested in the forms of inhibition of pathologic processes associated with any one of an immune-related disorder and a hepatic disorder, a significant reduction in their magnitude, or an improvement in a diseased subject
20 physiological state.

[00146] The term "inhibit" and all variations of this term is intended to encompass the restriction or prohibition of the progress and exacerbation of pathologic symptoms or a pathologic process progress, said pathologic process symptoms or process are associated with.

25 [00147] The term "eliminate" relates to the substantial eradication or removal of the pathologic symptoms and possibly pathologic etiology, optionally, according to the methods of the invention described below.

[00148] The terms "delay", "delaying the onset", "retard" and all variations thereof are intended to encompass the slowing of the progress and/or exacerbation of an immune-related
30 disorder or a hepatic disorder and their symptoms slowing their progress, further

exacerbation or development, so as to appear later than in the absence of the treatment according to the invention.

[00149] By “subject in need” or “patient” it is meant any mammal who may be affected by the above-mentioned conditions, and to whom the treatment and diagnosis methods herein described is desired, including human, bovine, equine, canine, murine and feline subjects. Preferably, the patient is a human. Administering of the composition according to the method of the invention to the patient includes both self-administration and administration to the patient by another person.

EXAMPLES

10 Experimental procedures

Animals

[00150] Male C57Bl/6 mice (11–12 weeks old) were obtained from Harlan Laboratories (Jerusalem, Israel) and maintained in the Animal Core of the Hadassah-Hebrew University Medical School. All mice were administered standard laboratory chow and water *ad libitum* and kept in a 12-hour light/dark cycle. The experiments were performed according to guidelines of the Hebrew University-Hadassah Institutional Committee for Care and Use of Laboratory Animals and after the Committee’s approval.

Concanavalin A

[00151] Concanavalin A solution (Con A; purchased from MP Biomedicals, USA) consisted of 2mg Con A in 1ml distilled water. Mice were intravenously (IV) injected with 250µl Con A solution (0.5 mg/mouse).

AST and ALT levels as parameters of liver damage

[00152] Mice were tested for serum alanine transaminase (ALT) and aspartate aminotransferase (AST) at 24 hours after Con A or acetaminophen administration. Serum AST and ALT levels were measured by an automatic analyzer.

5 [00153] **Experimental groups:** There were 3 experimental groups (A-C below), with 5 mice/group.

[00154] **Group A** (N=5) : Control, no anti-Eotaxin : Con A 500 µg/mouse, intravenous (iv);

[00155] **Group B** (N=5) : 200 ng anti-Eotaxin PO + after 2 hrs : Con A 500 µg/mouse,
10 iv;

[00156] **Group C** (N=5): 200 ng anti-Eotaxin intraperitoneal (IP) + after 2 hrs : Con A 500 µg/mouse, iv.

[00157] **PO and IP administration of anti-eotaxin-1 mAb** : anti-eotaxin-1 mAb (Recombinant Mouse CCL11/Eotaxin antibody, Catalog # 420-ME, R&D) was
15 administered at a dosage of 200 ng/mouse, 2 hours prior administration of Con A.

Table 1. Treatment Groups

<i>Group</i>	<i>Treatment/mouse</i>	<i>Vol/mouse</i>	<i>After 2 hrs : ConA</i>
A Control	-	100 µl	200 µl
B PO	200 ng anti-eotaxin PO	100 µl	200 µl
C IP	200 ng anti-eotaxin IP	100 µl	200 µl

Results

[00158] C57B1/6 mice were treated once with either oral or intra-peritoneal anti-eotaxin-1 antibody (200 ng/dose) two hours before induction of immune-mediated hepatitis using injection of Concanavalin A (ConA). Mice were followed for liver injury as manifested by liver enzymes and for the effect on eotaxin-1 serum levels. The effect of treatment was compared with untreated control mice.

[00159] Both oral (PO) and IP administration of anti-eotaxin-1 alleviated the ConA immune-mediated liver injury. This is manifested by a significant reduction in serum ALT and AST levels (Figure 1, Table 2). Serum ALT levels decreased to 1,807 u/L after oral anti-eotaxin-1 administration, compared with 19,025 u/L in untreated controls, and 3,657 u/L in mice treated with parenteral anti-eotaxin-1 ($p<0.005$) (Figure 1, Table 2). A similar beneficial effect was noted for AST serum levels that decreased to 3,032 u/L in orally treated mice, compared with 17,143 and 2,418 u/L, in untreated controls and parenteral-treated mice, respectively ($p<0.005$) (Figure 1, Table 2). A trend for reduced serum eotaxin-1 levels was noted in treated mice, from 594 pg/ml in the controls to 554 pg/ml ($P=0.08$), and 561 pg/ml ($P=0.06$) in orally and intraperitoneally treated mice respectively.

Table 2. Mean levels of ALT and AST in each treatment group.

<u>Treatment Groups</u>	<u>ALT (IU/L)</u>	<u>AST (IU/L)</u>
ConA	19,025	17,143
Oral eotaxin	1,807.4	3,032.4
IP eotaxin	3,657	2,418

[00160] **Conclusion:** Oral administration of the non-absorbable anti-eotaxin-1 antibody shows biological activity in the gut, and exerts a systemic immunomodulatory effect to alleviate immune-mediated hepatitis. The data suggests that testing for eotaxin-1 serum levels may identify patients with high-eotaxin-1 levels-associated NASH, and such patients may be successfully treated with an oral anti-eotaxin-1 such as Bertilimumab.

[00161] While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the
5 invention.

CLAIMS

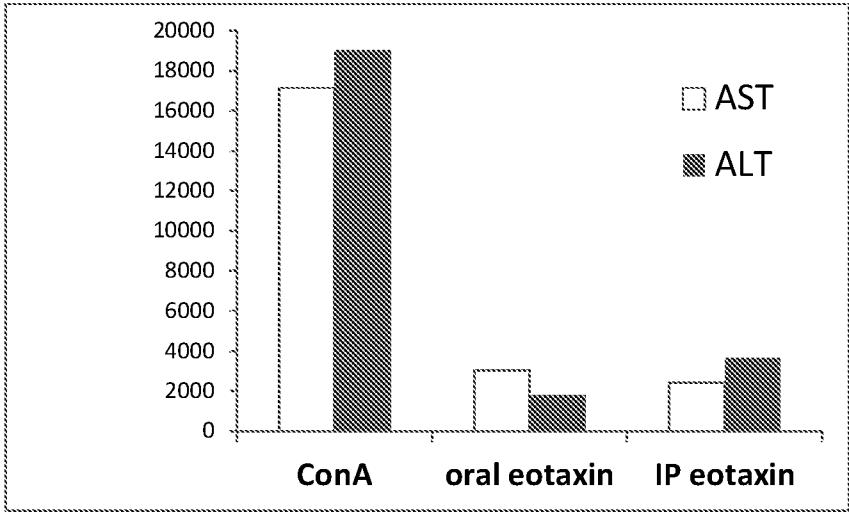
What is claimed is:

1. A composition comprising an inhibitor of anti-eotaxin-1 for use in a method for treating a subject suffering from a disorder associated with altered hepatic function and/or insulin resistance.
2. The composition of claim 1, wherein said method for treating a subject suffering from a disorder associated with altered hepatic function comprises improving or restoring hepatic function or liver function in said subject.
3. The composition of claim 1, wherein said method for treating a subject suffering from a disorder associated with altered hepatic function comprises reducing accumulation of fat in the liver in a subject.
4. The composition of claim 1, wherein said method for treating a subject suffering from a disorder associated with altered hepatic function comprises treating, improving, or suppressing liver damage in a subject.
5. The composition of claim 1, wherein said method for treating a subject suffering from a disorder associated with altered hepatic function comprises treating, improving, or suppressing steatosis in a subject.
6. The composition of any one of claims 1-5, wherein said subject has a liver disease.
7. The composition of claim 6, wherein said liver disease comprises nonalcoholic steatohepatitis (NASH).
8. The composition of any one of claims 6-7, wherein said liver disease comprises non-alcoholic fatty liver disease (NAFLD).
9. The composition of claim 6, wherein said liver disease comprises viral, bacterial, fungal or parasitic liver disease, alcoholic or autoimmune hepatitis, alcoholic or autoimmune cirrhosis, alcoholic fatty liver disease, alcoholic steatohepatitis (ASH), hepatocellular carcinoma, drug-induced liver disease, pediatric liver disease, metabolic liver disease, or a combination thereof.
10. The composition of claim 1, wherein said method for treating a subject suffering from a disorder associated with altered insulin resistance comprises treating, improving, or suppressing insulin resistance in said subject.

11. The composition of claim 1, wherein said method for treating a subject suffering from a disorder associated with altered insulin resistance comprises altering the insulin resistance state in said subject.
12. The composition of claim 1, wherein said method for treating a subject suffering from a disorder associated with altered insulin resistance comprises controlling blood sugar levels in a subject.
13. The composition of claim 12, wherein controlling blood sugar levels comprises inhibiting an increase in blood sugar levels.
14. The composition of claim 12, wherein controlling blood sugar levels comprises decreasing blood sugar levels.
15. The composition of claim 1, wherein said method for treating a subject suffering from a disorder associated with altered insulin resistance comprises improving glucose tolerance in a subject.
16. A composition comprising an inhibitor of anti-eotaxin-1 for treating, preventing, ameliorating, reducing or delaying the onset of, improving, or suppressing an immune-related disorder in a subject.
17. The composition of claim 16, wherein said immune-related disorder comprises an inflammatory disorder, an autoimmune disorder, an infection, a proliferative disorder, or a combination thereof.
18. A composition comprising an inhibitor of anti-eotaxin-1 for reducing inflammation in a subject.
19. A composition comprising an inhibitor of anti-eotaxin-1 for treating, improving, suppressing, preventing, ameliorating, reducing or delaying the onset of a toxic effect of a drug or compound in a subject.
20. The composition of claim 19, wherein said toxic effect is short-term.
21. The composition of claim 19, wherein said toxic effect is long-term.
22. A composition comprising an inhibitor of anti-eotaxin-1 for treating, preventing, ameliorating, reducing or delaying the onset of a neurological disorder in a subject comprising the step of administering a composition comprising an inhibitor of anti-eotaxin-1 to said subject.
23. The composition of claim 22, wherein said neurological disorder comprises Alzheimer's Disease.

24. A composition comprising an inhibitor of anti-eotaxin-1 for treating, preventing, ameliorating, reducing or delaying the onset of an acute or chronic disease in a subject that has high levels of eotaxin-1 in serum or in a tissue.
25. A composition comprising an inhibitor of anti-eotaxin-1 for enhancing or augmenting the therapeutic effect of a therapeutic agent in a subject.
26. The composition of any one of claims 1-25, wherein said inhibitor of eotaxin-1 is an anti-eotaxin antibody.
27. The composition of any one of claims 1-26, wherein said composition is formulated for non-parenteral administration.
28. The composition of claim 27, wherein said composition is formulated for oral, intra-nasal, intra-rectal, or intra-dermal administration.
29. The composition of any one of claims 1-28, wherein said method for treating said subject comprises preventing or alleviating symptoms related to the condition.
30. The composition of any one of claims 1-29, wherein said subject suffers from pre-diabetes, diabetes, weight gain, obesity, pancreatic dysfunction, pancreatic inflammation, alcohol intoxication, alcohol withdrawal, a condition associated with alteration of pancreatic or liver function, a condition associated with tissue or organ damage, drug-induced hepatic dysfunction, or a combination thereof.
31. The composition of any one of claims 1-29, wherein said subject suffers from a metabolic syndrome, vertigo, an inflammation of pancreas, liver, muscle or the adipose tissue, inflammatory disorder, a malignancy, or a combination thereof.
32. The composition of any one of claims 1-31, further comprising an additional therapeutic agent.
33. The composition according to claim 32, wherein said additional therapeutic agent is formulated to be administered concurrently or in parallel with said inhibitor of anti-eotaxin-1.
34. The composition according to any one of claims 32-33, wherein said additional therapeutic agent is a treatment for NASH, diabetes, obesity, or an immune associated disease.
35. The composition of any one of claims 1-34, wherein said subject has high serum levels of eotaxin-1.

36. The composition of any one of claims 1-35, wherein said subject has high tissue levels of eotaxin-1.
37. A kit comprising an inhibitor of anti-eotaxin-1 and instructions for use.



	ConA, oral	ConA, IP	oral, IP
ALT	0.000000009	0.0000003	0.00099
AST	0.00006	0.0000003	0.35466

FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2017/050637

A. CLASSIFICATION OF SUBJECT MATTER IPC (2017.01) A61K 39/395, A61P 1/16, C07K 16/24 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC (2017.01) A61K, A61P, C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Databases consulted: NCBI, Esp@cenet, Google Patents, CAPLUS, BIOSIS, EMBASE, MEDLINE, PubMed, Google Scholar, DWPI, Derwent Innovation Search terms used: Bertilimumab, Eotaxin, antibody, hepatic, liver, YARON, Ilan, ccl11, Chemokine, MPIF		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0166754 A1 CAMBRIDGE ANTIBODY TECH?[GB] 13 Sep 2001 (2001/09/13) Abstract, page 26 last paragraph, pages 27 – 30	1-9,26-37
A	L de Graaf, K., H Kosco-Vilbois, M., & Fischer, N. (2012). Therapeutic targeting of chemokines with monoclonal antibodies. Current Immunology Reviews, 8(2), 141-148. http://www.ingentaconnect.com/contentone/ben/cir/2012/00000008/00000002/art00005?crawler=true&mimetype=application/pdf 01 May 2012 (2012/05/01) From page 143 right column line 4 to page 144 left column line 24, table 1	1-9,26-37
A	Legrand, F., & Klion, A. D. (2015). Biologic therapies targeting eosinophils: current status and future prospects. The Journal of Allergy and Clinical Immunology: In Practice, 3(2), 167-174. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4418449/pdf/nihms-662071.pdf 01 Mar 2016 (2016/03/01) Page 6 of Author Manuscript third paragraph, table 1	1-9,26-37
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 08 Aug 2017		Date of mailing of the international search report 14 Sep 2017
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Facsimile No. 972-2-5651616		Authorized officer AXELRAD Itschak Telephone No. 972-2-5651648

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2017/050637

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Levina, V., Nolen, B. M., Marrangoni, A. M., Cheng, P., Marks, J. R., Szczepanski, M. J., ... & Lokshin, A. E. (2009). Role of eotaxin-1 signaling in ovarian cancer. <i>Clinical Cancer Research</i>, 15(8), 2647-2656. http://clincancerres.aacrjournals.org/content/clincanres/15/8/2647.full.pdf 15 Apr 2008 (2008/04/15) Abstract, page 7 of Author Manuscript third paragraph, page 10 of Author Manuscript third and last paragraphs, fig 2A and 2B	1-9,26-37
A	Nolen, B. M., & Lokshin, A. E. (2010). Targeting CCL11 in the treatment of ovarian cancer. <i>Expert opinion on therapeutic targets</i>, 14(2), 157-167. http://www.tandfonline.com/doi/abs/10.1517/14728220903512983 08 Jan 2010 (2010/01/08) Abstract	1-9,26-37
A	Zhang, Z., Cherryholmes, G., Mao, A., Marek, C., Longmate, J., Kalos, M., ... & Shively, J. E. (2008). High plasma levels of MCP-1 and eotaxin provide evidence for an immunological basis of fibromyalgia. <i>Experimental biology and medicine</i>, 233(9), 1171-1180. http://fmcfsme.com/documents/City%20of%20Hope%20Reprint.pdf 05 Jun 2008 (2008/06/05) Abstract, table 2, Figs. 1-2, page 1179 left column last paragraph	1-9,26-37

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2017/050637

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-9,26-37

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet):

* This International Searching Authority found multiple inventions in this international application, as follows:

Invention/s 1	Claim No. 1, 26-37 (partially), claims Nos. 2-9 (whole). Relates to a composition comprising an anti-eotaxin-1 for use in a method for treating a subject suffering from a disorder associated with altered hepatic function and relates also to a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use (in a method for treating a subject suffering from a disorder associated with altered hepatic function).	Claim/s 1-9,26-37
Invention/s 2	Claim No. 1, 26-37 (partially), claims Nos. 10-15 (whole). Relates to a composition comprising an anti-eotaxin-1 for use in a method for treating a subject suffering from a disorder associated with insulin resistance and relates also to a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use (in a method for treating a subject suffering from a disorder associated with insulin resistance).	Claim/s 1,10-15,26-37
Invention/s 3	Invention 3: Claims Nos. 16-17 (whole), Claim No. 26-37 (partially). Relates to a composition comprising an anti-eotaxin-1 for treating, preventing, ameliorating, reducing or delaying the onset of, improving, or suppressing an immune-related disorder in a subject and relates also to a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use (for treating, preventing, ameliorating, reducing or delaying the onset of, improving, or suppressing an immune-related disorder in a subject).	Claim/s 16,17,26-37
Invention/s 4	Claim No. 18 (whole), Claim No. 26-37 (partially). Relates to a composition comprising an anti-eotaxin-1 for reducing inflammation in a subject and relates also to a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use (for reducing inflammation in a subject).	Claim/s 18,26-37
Invention/s 5	Claims Nos. 19-21 (whole), Claim No. 26-37 (partially). Relates to a composition comprising an anti-eotaxin-1 for treating, improving, suppressing, preventing, ameliorating, reducing or delaying the onset of a toxic effect of a drug or compound in a subject and relates also to a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use (for treating, improving, suppressing, preventing, ameliorating, reducing or delaying the onset of a toxic effect of a drug or compound in a subject).	Claim/s 19-21,26-37
Invention/s 6	Claims Nos. 22-23 (whole), Claim No. 26-37 (partially). Relates to a composition comprising an anti-eotaxin-1 for treating, preventing, ameliorating, reducing or delaying the onset of a neurological disorder in a subject comprising the step of administering a composition comprising an anti-eotaxin-1 to said subject and relates also to a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use (for treating, preventing, ameliorating, reducing or delaying the onset of a neurological disorder in a subject comprising the step of administering a composition comprising an anti-eotaxin-1 to said subject).	Claim/s 22,23,26-37

Invention/s 7 Claim No. 24 (whole), Claim No. 26-37 (partially). Claim/s 24,26-37

Relates to a composition comprising an anti-eotaxin-1 for treating, preventing, ameliorating, reducing or delaying the onset of an acute or chronic disease in a subject that has high levels of eotaxin-1 in serum or in a tissue and relates also to a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use (for treating, preventing, ameliorating, reducing or delaying the onset of an acute or chronic disease in a subject that has high levels of eotaxin-1 in serum or in a tissue).

Invention/s 8 Claim No. 25 (whole), Claim No. 26-37 (partially). Claim/s 25-37

Relates to a composition comprising an anti-eotaxin-1 for enhancing or augmenting the therapeutic effect of a therapeutic agent in a subject and relates also to a kit comprising an inhibitor of anti-eotaxin-1 and instructions for use (for enhancing or augmenting the therapeutic effect of a therapeutic agent in a subject).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2017/050637

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