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(54) Title: AGENTS FOR INCREASING THE SECRETION OF ANTI-INFLAMMATORY CYTOKINES

(57) Abstract: The authors of the present invention have found a method for enhancing the endogenous production of anti-inflammatory cytokines, such as interleukin-10 (IL-10), in mammalian cells or tissues, comprising administering to a subject, preferably a human subject, in need thereof an effective amount of a LRH-1 agonist according to the invention or a pharmaceutically acceptable salt thereof. This method is shown in the present specification as particularly suitable for treating diseases wherein immunomodulation by an increase in the secretion of anti-inflammatory cytokines, such as IL-10, is desirable, for instance for the treatment of cancer and anti-inflammatory diseases such as type I diabetes, in particular early stage type I diabetes, type II diabetes and autoimmune hepatitis.



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Agents for increasing the secretion of anti-inflammatory cytokines

Field of the invention

The present invention relates to compounds and compositions increasing the secretion of anti-inflammatory cytokines and methods using thereof for treating cancer or an inflammatory disease or condition in a subject in need thereof.

More particularly, the present invention relates to the use of an effective amount of a LRH-1 agonist according to the invention or a pharmaceutically acceptable salt thereof for treating cancer or an inflammatory disease or condition in a subject in need thereof.

Background of the invention

Inflammation is a physiological condition characterized in the acute form by the classical signs of pain, heat, redness, swelling and loss of function. Inflammation often accompanies diseases such as Multiple Sclerosis (MS), osteoarthritis, Inflammatory Bowel Disease (IBD) including Crohn's disease and ulcerative colitis, Rheumatoid Arthritis (RA), atherosclerosis, encephalomyelitis, Alzheimer's disease, stroke, traumatic brain injury, Parkinson's disease and others. In most cases, there is no effective cure for inflammation associated with such disease and existing treatments are palliative and largely fail to control the underlying causes of tissue degradation.

In fact, although an armada of anti-inflammatory drugs for the treatment of immune diseases such as arthritis are available on the market, these compounds merely transiently reduce inflammation and do not block the immune attack. In addition, natural compounds such as Honokiol or cinnamaldehyde isolated from the bark of houpou and the leaves of Cinnamomum osmophloeum respectively were shown to inhibit LPS induced pro-inflammatory cytokines secretion from monocytes/macrophage. However, to the best of our knowledge, these compounds do not stimulate production of anti-inflammatory cytokines.

Therefore, there is a need to find compounds, which could be used as immunomodulators for the treatment and prevention of any inflammatory disease including diabetes mellitus.

Many treatments are available for cancer, including surgery and radiation for localised disease, and chemotherapy. However, the efficacy of available treatments for many cancer types is limited, and new, improved forms of treatment showing clinical benefits are needed. This is especially true for those patients presenting advanced and/or metastatic disease and for patients relapsing after having been treated with established therapies which become ineffective

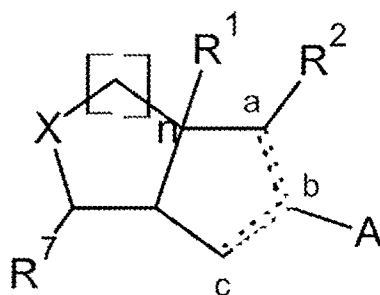
or intolerable due to acquisition of resistance or to limitations in administration of the therapies due to associated toxicities.

Since cancer is a leading cause of death in animals and humans, there is still a need to obtain a safe and effective therapy to be administered to patients suffering from a cancer.

Brief description of the invention

The authors of the present invention have found a method for enhancing the endogenous production of anti-inflammatory cytokine interleukin-10 (IL-10) in mammalian cells or tissues, comprising administering to a subject, preferably a human subject, in need thereof an effective amount of a LRH-1 agonist according to the invention or a pharmaceutically acceptable salt thereof. This method is shown in the present specification as particularly suitable for treating diseases wherein immunomodulation by an increase in the secretion of anti-inflammatory cytokines, such as IL-10, is desirable, for instance for the treatment of cancer, and anti-inflammatory diseases such as type I diabetes, in particular early stage type I diabetes, type II diabetes and autoimmune hepatitis.

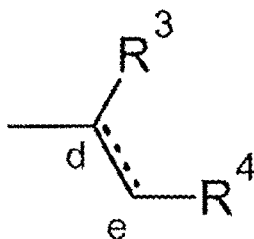
Consequently, a first aspect of the invention refers to a LRH-1 agonist; wherein said agonist is a 9-substituted bicycle [3.3.0] octane derivative of the following formula



Formula I

wherein

A is methyl, ethyl, aryl, cycloalkyl or



X is $C(R)_2$ or NR;

n is 1 or 2;

R is H, alkyl or R is OR¹⁰ wherein R¹⁰ is H, alkyl, acyl;

R¹ is -N(R⁵)₂, OR¹¹ or C(R¹²)=CH₂;

R² is H, alkyl, halogen, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene or N-heterocyclyl which can be optionally substituted;

R³ and R⁴ are independently H, alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene, halogen or N-heterocyclyl;

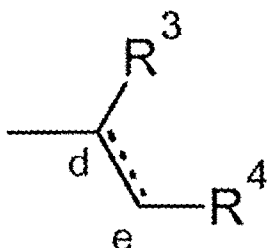
each R⁵ is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl or aralkenyl;

R⁷ is H, OH, OR⁸ wherein R⁸ is alkyl, acyl or aryl; and

R¹¹ is C₂-C₄ optionally substituted C₂-C₄ alkyl, optionally substituted aralkyl, optionally substituted cycloalkyl;

R¹² is optionally substituted aryl or R¹² is C₂-C₄ alkyl;

wherein when A is



there is independently a maximum of one double bond between each of the carbon atoms of the centers a-b and b-c and d-e;

and when A is methyl, aryl or cycloalkyl there is independently a maximum of one double bond between each of the carbon atoms of the centers a-b and b-c;

for use in a method of increasing the secretion of anti-inflammatory cytokines, such as IL-10, in the leukocytes of a subject in need thereof suffering from cancer or from an inflammatory disease or condition.

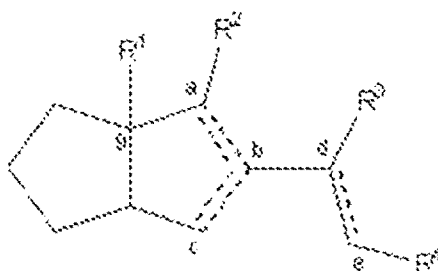
In a related aspect, the invention refers to a LRH-1 agonist according to the invention or a pharmaceutically acceptable salt thereof for use in the treatment of a subject suffering from cancer or from an inflammatory disease or condition. In a further related aspect, the invention refers to the use of a LRH-1 agonist according to the invention or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in the treatment of a subject suffering from cancer or from an inflammatory disease or condition. In an additional related aspect, the invention refers to a method for the treatment a subject suffering from cancer or from an inflammatory disease or condition, that comprises administering to the subject or patient a therapeutically effective amount of a LRH-1 agonist according to the invention or a

pharmaceutically acceptable salt thereof. These are collectively referred as the first aspect of the invention.

In a particular embodiment of the first aspect of the invention, the LRH-1 agonist according to the invention or a pharmaceutically acceptable salt thereof is capable of increasing the secretion of anti-inflammatory cytokines, such as IL-10, in the leukocytes of a subject.

In another particular embodiment of the first aspect of the invention, the LRH-1 agonist according to the invention or a pharmaceutically acceptable salt thereof is capable of increasing the number of immune cells with an anti-inflammatory profile, preferably wherein said cells are selected from the group consisting of T regs, Th2 cells and M2 macrophages.

In a preferred embodiment of the first aspect of the invention, said agonist is a 9-substituted bicycle [3.3.0] octane derivative having formula II



Formula II

wherein

R^1 is $-N(R^5)_2$;

R^2 is H, alkyl, halogen, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene or N-heterocyclyl which can be optionally substituted

R^3 and R^4 are independently alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene, halogen or N-heterocyclyl;

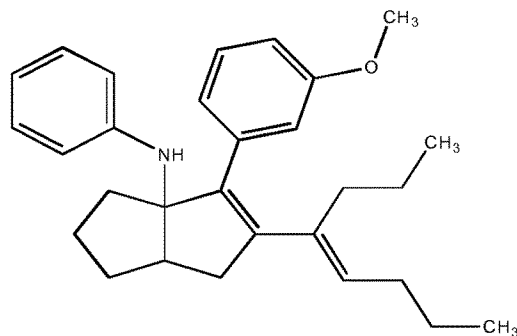
each R^5 is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl or aralkenyl;

and

each R^6 is a straight or branched alkylene chain optionally substituted by hydroxy, mercapto, alkylthio, aryl, cycloalkyl, $-N(R^5)_2$, $-C(=O)OR^5$ or $-C(=O)N(R^5)_2$; and

wherein there is independently a maximum of one double bond between each of the carbon atoms of the centers a-b and b-c and d-e.

In another preferred embodiment of the first aspect of the invention, said agonist is a 9-substituted bicyclo [3.3.0] octane derivative having formula III



or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the first aspect of the invention, the subject in need thereof suffers from an inflammatory disease or condition selected from the list consisting of: Acute Disseminated Encephalomyelitis (ADEM); Acute necrotizing hemorrhagic leukoencephalitis; Addison's disease; Agammaglobulinemia; Alopecia areata; Amyloidosis; Ankylosing spondylitis; Anti-GBM/Anti-TBM nephritis; Antiphospholipid syndrome (APS); Autoimmune angioedema; Autoimmune aplastic anemia; Autoimmune dysautonomia; Autoimmune hepatitis; Autoimmune hyperlipidemia; Autoimmune immunodeficiency; Autoimmune inner ear disease (AIED); Autoimmune myocarditis; Autoimmune oophoritis; Autoimmune pancreatitis; Autoimmune retinopathy; Autoimmune thrombocytopenic purpura (ATP); Autoimmune thyroid disease; Autoimmune urticarial; Axonal & neuronal neuropathies; Balo disease; Behcet's disease; Bullous pemphigoid; Cardiomyopathy; Castleman disease; Celiac disease; Chagas disease; Chronic fatigue syndrome; Chronic inflammatory demyelinating polyneuropathy (CIDP) ; Chronic recurrent multifocal osteomyelitis (CRMO); Churg-Strauss syndrome; Cicatricial pemphigoid/benign mucosal pemphigoid; Crohn's disease; Cogans syndrome; Cold agglutinin disease; Congenital heart block; Coxsackie myocarditis; CREST disease; Essential mixed cryoglobulinemia; Demyelinating neuropathies; Dermatitis herpetiformis; Dermatomyositis; Devic's disease (neuromyelitis optica) ; Discoid lupus; Dressler's syndrome; Endometriosis; Eosinophilic esophagitis; Eosinophilic fasciitis; Erythema nodosum; Experimental allergic encephalomyelitis; Evans syndrome; Fibromyalgia; Fibrosing alveolitis; Giant cell arteritis (temporal arteritis); Giant cell myocarditis; Glomerulonephritis; Goodpasture's syndrome; Granulomatosis with Polyangiitis (GPA) (formerly called Wegener's Granulomatosis); Graves' disease; Guillain-Barre syndrome; Hashimoto's encephalitis; Hashimoto's thyroiditis; Hemolytic anemia; Henoch-Schönlein purpura; Herpes gestationis; Hypogammaglobulinemia; Idiopathic thrombocytopenic purpura (ITP); IgA nephropathy; IgG4-related sclerosing disease; Immunoregulatory lipoproteins; Inclusion body myositis; Interstitial cystitis; Juvenile arthritis; Juvenile myositis; Kawasaki syndrome; Lambert-Eaton syndrome; Leukocytoclastic vasculitis;

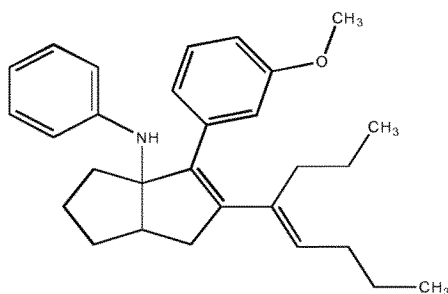
Lichen planus; Lichen sclerosus; Ligneous conjunctivitis; Linear IgA disease (LAD); Lupus (SLE); Lyme disease, chronic Meniere's disease; Microscopic polyangiitis; Mixed connective tissue disease (MCTD); Mooren's ulcer; Mucha-Habermann disease; Multiple sclerosis; Myasthenia gravis; Myositis; Narcolepsy; Neuromyelitis optica (Devic's); Neutropenia; Ocular cicatricial pemphigoid; Optic neuritis; Palindromic rheumatism; PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus); Paraneoplastic cerebellar degeneration; Paroxysmal nocturnal hemoglobinuria (PNH); Parry Romberg syndrome; Parsonnage-Turner syndrome; Pars planitis (peripheral uveitis); PemphigusPeripheral neuropathy; Perivenous encephalomyelitis; Pernicious anemia; POEMS syndrome; Polyarteritis nodosaType I, II, & III autoimmune polyglandular syndromes; Polymyalgia rheumatica; Polymyositis; Postmyocardial infarction syndrome; Postpericardiotomy syndromeProgesterone dermatitis; Primary biliary cirrhosis; Primary sclerosing cholangitis; Psoriasis; Psoriatic arthritis; Idiopathic pulmonary fibrosis; Pyoderma gangrenosum; Pure red cell aplasia; Raynauds phenomenon; Reactive Arthritis; Reflex sympathetic dystrophy; Reiter's syndrome; Relapsing polychondritis; Restless legs syndrome; Retroperitoneal fibrosis; Rheumatic fever; Rheumatoid arthritis; Sarcoidosis; Schmidt syndrome; Scleritis; Scleroderma; Sjogren's syndrome; Sperm & testicular autoimmunity; Stiff person syndrome; Subacute bacterial endocarditis (SBE); Susac's syndrome; Sympathetic ophthalmia; Takayasu's arteritis; Temporal arteritis/Giant cell arteritis; Thrombocytopenic purpura (TTP); Tolosa-Hunt syndrome; Transverse myelitis; Ulcerative colitis; Undifferentiated connective tissue disease (UCTD); UveitisVasculitis; Vesiculobullous dermatosis; VitiligoWegener's granulomatosis (now termed Granulomatosis with Polyangiitis (GPA)).

In another preferred embodiment of the first aspect of the invention, the subject in need thereof suffers from a disease selected from the list consisting of type I diabetes, in particular early stage type I diabetes, type II diabetes and autoimmune hepatitis. In the context of the present invention, early stage type I diabetes is defined as the stages of the disease wherein one or all of the following criteria can be detected:

- a. Detection of islet cell autoantibodies and/or antibodies to insulin, GAD65, and tyrosine phosphatases IA-2 and IA-2beta;
- b. Detection of ketoacidosis; and
- c. Detection of hyperglycemia.

In a preferred embodiment of the first aspect of the invention, the subject in need thereof suffers from type II diabetes and said agonist is use for the therapeutic treatment after the clinical manifestation of the disease and not for the prophylactic treatment of type II diabetes.

In a still more preferred embodiment of the first aspect of the invention, said agonist is a 9-substituted bicyclo [3.3.0] octane derivative having formula III



Formula III

or a pharmaceutically acceptable salt thereof and the subject in need thereof suffers from a disease selected from the list consisting of type I diabetes, in particular early stage type I diabetes, type II diabetes and autoimmune hepatitis.

In another preferred embodiment of the first aspect of the invention, the agonist is administered to the subject, preferably a human subject, in need thereof via oral, intraarterial or intravenously.

A second aspect of the invention refers to a method for enhancing the endogenous production of interleukin-10 (IL-10) in mammalian cells or tissues, comprising administering to a subject in need thereof an effective amount of a compound, as defined in the first aspect of the invention or in any of its preferred embodiments, or a pharmaceutically acceptable salt thereof.

A third aspect of the invention refers to a method for treating type I diabetes, in particular early stage type I diabetes, type II diabetes or autoimmune hepatitis, comprising administering to a subject in need thereof an effective amount of a compound, as defined in the first aspect of the invention or in any of its preferred embodiments, or a pharmaceutically acceptable salt thereof.

A fourth aspect of the invention refers to the LRH-1 agonist as defined in any of the precedent aspects or preferred embodiments, for use in a method of improving glucose tolerance in a subject in need thereof suffering from type II diabetes. Alternatively, this aspect of the invention refers to a method for improving glucose tolerance in a subject suffering from type II diabetes comprising administering to said subject in need thereof an effective amount of a compound according to any of claims 1 to 3 or a pharmaceutically acceptable salt thereof.

Brief description of the figures

FIG. 1: BL001 reduces the incidence of hyperglycemia in immunized RIP-B7.1 mice. (A) RIP-B7.1 mice were either pre-treated or not for 5 days with BL001 or the vehicle. Half the animals were then immunized with a preproinsulin II encoding plasmid to induce the autoimmune response. BL001 or vehicle-treated animals were injected daily for up to 8 weeks.

(B) Blood glucose levels were measured weekly. Results are presented as % of animals that developed hyperglycemia as compared to the total number of animals in each group: NT (not treated), $n=12-24$; Vehicle, $n=12-24$; BL001, $n=12-24$; Immunized, $n=34-43$; Immunized/Vehicle, $n=12-24$; Immunized/BL001, $n=26-38$.

FIG. 2: BL001 pretreatment reduces islet inflammation and preserves β -cell mass in immunized RIP-B7.1 mice. Pancreas sections obtained from immunized or not and vehicle or BL001-treated RIP-B7.1 mice 8-weeks post-treatment were either stained with **(A)** Hematoxylin and Eosin (H&E) or **(B)** co-immunostained for glucagons (GLUC, green) and insulin (INS, red). Nuclei were stained with DAPI.

FIG. 3: The incidence of hyperglycaemia in autoimmune sensitized RIP-B7.1 mice is reduced by 50 % subsequent to BL001 treatment: **(A)** Eight week-old RIP-B7.1 mice were immunized at day 0 (week 0) and then 7 days later (week 1) with a DNA plasmid expressing preproinsulin II to induce a robust autoimmune response. Animals were then injected daily starting at week 1 for up to 8 weeks with either vehicle (black line) or BL001 (green line). **(B)** Glucose levels were measured weekly from a tail vein blood sample. Results are presented as % of animals that developed hyperglycemia as compared to the total number of animals in each group.

FIG. 4: BL001-treated and immunized RIP-B7.1 mice niche auto-reactivated T-cells to ppINS. Spleens were extracted at the indicated time points from random immunized (ppINS) RIP-B7.1 mice that were treated or not with BL001. A splenocyte proliferation assay using [^3H] Thymidine incorporation was performed in order to assess the presence of ppINS auto-reactivated T-cells. The proliferation of splenocytes isolated from control untreated animals at week 4, 6 and 8 and exposed in vitro to the ppINS peptide was comparable and thus combined into 1 group. Similarly, proliferation of splenocytes derived from RIP-B7.1 mice treated with BL001 prior (Cohort A) or subsequent (Cohort B) to ppINS immunization was identical for each time point and therefore both cohort were considered as one for the corresponding time point. Results are expressed as fold change as compared to non-ppINS peptide-treated splenocytes. * $p<0.05$ and ** $p<0.01$ as compared to control (first bar).

FIG. 5: BL001 potentiates the LPS-induced cytokine profile of the mouse macrophage RAW264.7 cell line. RAW264.7 cells were incubated for 24 hours with increasing concentrations of BL001 alone or in combination with the cytokine activating compound lipopolysaccharide (LPS). (A) Cell viability (MTT assay) and (B) proliferation were assessed by MTT assay and BrdU incorporation. (C) The Cytokine secretion profile was measured using proprietary electrochemiluminescence technology from MSD.

FIG. 6: BL001-treatment improves glucose tolerance in mice fed a high fat diet. (A) Eight week-old C57/bl6 mice were fed a high fat diet (HFD) for up to 20 weeks. BL001 administration was initiated at week 16, time at which animals exhibited signs of glucose intolerance. **(B)** A glucose tolerance test performed at week 20 reveals that BL001-treated animals on the HFD display improved glucose sensitivity as compared to control animals.

FIG 7: BL001 reverts insulinitis by increasing levels of IL10, IL6 and IL5. RIP-B7.1 mice were pre-treated or not with BL001 for 5 days and then immunized or not with a ppINSII cDNA containing plasmid. Treatment with BL001 was pursued for an additional 8 weeks. Mice were killed at 4 and 8 weeks, pancreas extracted and processed for histology and flow cytometry analysis. Insulinitis scoring was performed at **(A)** 4 and **(B)** 8 weeks as a grade of 0 to 4 according to percentage of infiltrated islet area (0, no infiltration, 1, minimal focal infiltration, 2, peri-islet infiltration, 4, extensive infiltration.). $n=5-6$. Blood samples were collected from control or immunized RIP-B7.1 mice treated or not with BL001 for up to 8 weeks. **(C)** IL10, **(D)** IL5 and **(E)** IL6 levels were then assessed using the mouse V-PLEX ProInflammatory Panel 1 kit 10-Plex from Meso Scale Discovery (MSD). Detection was performed using proprietary electrochemiluminescence technology and data acquired on a MESOTM QuickPlex SQ120 (MSD). Anova ** $p<0.01$ and *** $p<0.001$. C; control, BL; BL001, IMN; immunized and BL IMN; BL001 treated and immunized.

FIG 8: BL001 treated and immunized RIP-B7.1 mice display an increase in the percentage of pancreatic Th2 cells. Pancreatic **(A)** T regulatory cells (Treg), **(B)** T helper cells type 1 (Th1), **(C)** Th2 and **(D)** Th17 were assessed by flow cytometry. Anova * $p<0.05$ and ** $p<0.01$. C; control, BL; BL001, IMN; immunized and BL IMN; BL001 treated and immunized.

FIG 9: BL001 dose-dependently increases IL4 secretion from the mouse macrophage RAW264.7 cell line exposed to increasing concentrations of LPS. RAW264.7 cells were incubated for 24 hours with increasing concentrations of BL001 alone or in combination with **(A)** 0.25 ug/ml, **(B)** 0.5 ug/ml and **(C)** 1.0 ug/ml of the cytokine activating compound lipopolysaccharide (LPS). IL-4 secretion was measured using proprietary electrochemiluminescence technology from MSD. Anova * $p<0.05$ and **** $p<0.0001$.

FIG 10: BL001 promotes an anti-inflammatory environment. BL001 increases circulating levels of IL10, IL5 and to a lesser extent IL6 that will promote expansion and differentiation of anti-inflammatory cell subsets that include Treg, Th2 and M2. These cells will in turn secrete IL10 and IL4 further favouring an anti-inflammatory environment. Dash line depicts unconfirmed secretion of IL10 or IL4.

FIG. 11: BL001-treated C57/bl6 mice are protected against streptozotocin (STZ)-induced hyperglycemia. A single high dose of STZ (150 mg / Kg body weight) was administered in either control (C STZ) or BL001 (BL STZ)-treated mice. Animals received a 5-day BL001 pre-treatment prior to STZ injection. (A) Blood glucose levels were measured weekly for up to four weeks and (B) hyperglycaemic incidence was determined for each group.

Detailed description of the invention

The present invention relates to compounds and compositions increasing the secretion of anti-inflammatory cytokines and methods using thereof for treating cancer or an inflammatory disease or condition in a subject in need thereof. In particular, the present invention relates to LRH-1 agonists as defined in the specification, for use in a method of increasing the secretion of anti-inflammatory cytokines, such as IL-10, in the leukocytes of a subject in need thereof suffering from cancer or an inflammatory disease or condition.

The principles and operation of the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details set forth in the following description or exemplified by the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

A "subject" when used herein includes mammalian and non-mammalian subjects. "Mammal" for purposes of treatment refers to any animal classified as a mammal, including human, domestic and farm animals, non-human primates, and any other animal that has mammary tissue. A mammal includes human, rodents such as mouse, rat or rabbit, sheep, cattle, goat, dog, cat, chimpanzee, horse, pig, etc., with human being preferred. A subject also includes human and veterinary patients, with human patients being preferred.

As used herein, the terms "LRH-1", "liver receptor homolog 1 ligand binding domain polypeptide", "LRH-1 ligand binding domain polypeptide", and "LRH-1 LBD polypeptide" (and like terms) are defined as illustrated in WO2011/144725. In particular, for human LRH-1, such domain generally includes residues A253 through A495 of NP_003813 encoded by NM_003822. For mouse LRH-1, such sequence generally extends from A318 through A560 of the protein encoded by NM_030676. An exemplary such human domain polypeptide is the polypeptide used for crystallization herein consisting of residues S251 -A495 of NP_003822 (see US 2006/0160135); additional examples include homologs and variants thereof. When used in the context of the present application the term "LRH-1" includes a LRH-1 (also

known as NR5A2, CPF or FTF) polynucleotide or polypeptide having a nucleotide or amino acid sequence, respectively, as is known in the art; see NM_003822 (cDNA sequence for hLRH-1 isoform 2), NP_003813 (protein sequence for hLRH-1 isoform 2), NM_205860 (cDNA sequence for hLRH-1 isoform 1), and NP_995582 (protein sequence for hLRH-1 isoform 1). When referring herein to LRH-1 nucleotide sequences or LRH-1 amino acid sequences, the aforementioned sequences are preferred as "reference sequences" when, e.g. determining the degree of identity of nucleotide or amino acid sequences which are encompassed by the term "LRH-1 ". The term "LRH-1 " also includes nucleotide sequences which are 60, 70, 80, 90, 95, 97, 98, 99% identical to the LRH-1 nucleotide sequences which are known in the art and described herein, wherein these 60, 70, 80, 90, 95, 97, 98, 99% identical nucleotide sequences encode a LRH-1 polypeptide which retains the activity as described herein. The nucleotide sequences according to the invention may be any type of nucleic acid, e.g. DNA, RNA or PNA (peptide nucleic acid).

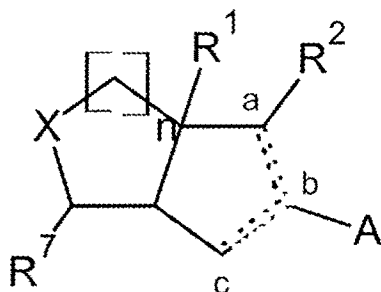
The term "LRH-1 " also includes amino acid sequences which are 60, 70, 80, 90, 95, 97, 98, 99% identical to the LRH-1 amino acid sequences which are known in the art and described herein, wherein these 60, 70, 80, 90, 95, 97, 98, 99% identical amino acid sequences retain the activity of LRH-1 as described herein. Said term also includes LRH-1 polypeptide variants having an amino acid sequence, wherein in such variants one or more, preferably 2, 4, 6, 8, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530 or 540 amino acids are added, deleted and/or substituted as long as such LRH-1 polypeptide variants retain the activity as described herein. Said term also includes LRH-1 polypeptide fragments, preferably of 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530 or 540 amino acids in length, wherein such fragments retain the activity as described herein.

LRH-1 homologs which are also included by the term "LRH-1" can be identified by their sequences, where exemplary reference sequence accession numbers are NM_003822 (cDNA sequence for hLRH-1 isoform 2), NP_003813 (protein sequence for hLRH-1 isoform 2), NM_205860 (cDNA sequence for hLRH-1 isoform 1), and NP_995582 (protein sequence for hLRH-1 isoform 1). One of ordinary skill in the art will recognize that sequence differences will exist due to allelic variation, and will also recognize that other animals, particularly other mammals, have corresponding receptors, which have been identified or can be readily identified using sequence alignment and confirmation of activity, which can also be used. A number of such sequences are readily available from GenBank. One of ordinary skill in the art will also recognize that modifications can be introduced in a LRH-1 sequence without destroying

receptor activity. Such modified receptors can also be used in the present invention, e.g., if the modifications do not alter the binding site conformation to the extent that the modified receptor lacks substantially normal ligand binding.

The term "LRH-1 agonist" means an agent or a compound that increases, supplements, or potentiates the bioactivity of LRH-1. Preferably, an LRH-1 agonist interacts directly or indirectly with LRH-1 and initiates a physiological and/or a pharmacological response characteristic of LRH-1. An LRH-1 agonist is believed to increase, supplement, or potentiate the activity of LRH-1 or the expression of LRH-1 either directly or indirectly. The action of an LRH-1 agonist can, for example, occur at the protein level. Particularly, LRH-1 may interact with the agonist such that it is more active. The action of an LRH-1 agonist may, however, also occur on nucleic acid level. Namely, the LRH-1 gene is transcribed more frequently giving rise to more protein. The action of an LRH-1 agonist may also influence RNA or protein stability. A direct interaction via binding of the agonist to LRH-1 is, however, preferred. Though less preferred, it is nevertheless envisaged that an LRH-1 agonist may act as an agonist of SF-1, i.e., act as an SF-1 agonist. Preferably, the term "agonists", in accordance with this invention, are understood as defined in paragraphs [0039] to [0092] of WO 2011/144725.

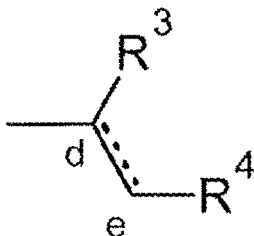
Preferably, the LRH-1 agonist applied in the uses and methods of the invention is a 9-substituted bicyclo [3.3.0] octane derivative of the following formula



Formula I

wherein

A is methyl, ethyl, aryl, cycloalkyl or



X is C(R)₂ or NR;

n is 1 or 2;

R is H, alkyl or R is OR¹⁰ wherein R¹⁰ is H, alkyl, acyl;

R¹ is -N(R⁵)₂, OR¹¹ or C(R¹²)=CH₂;

R² is H, alkyl, halogen, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene or N-heterocyclyl which can be optionally substituted;

R³ and R⁴ are independently H, alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene, halogen or N-heterocyclyl;

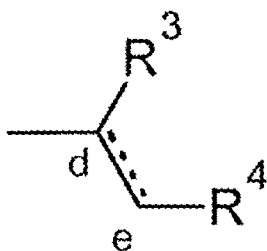
each R⁵ is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl or aralkenyl;

R⁷ is H, OH, OR⁸ wherein R⁸ is alkyl, acyl or aryl; and

R¹¹ is C₂-C₄ optionally substituted C₂-C₄ alkyl, optionally substituted aralkyl, optionally substituted cycloalkyl;

R¹² is optionally substituted aryl or R¹² is C₂-C₄ alkyl;

wherein when A is



there is independently a maximum of one double bond between each of the carbon atoms of the centers a-b and b-c and d-e

and when A is methyl, aryl or cycloalkyl there is independently a maximum of one double bond between each of the carbon atoms of the centers a-b and b-c.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (iso-propyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), and the like. Unless stated otherwise specifically in the specification, the alkyl radical may be optionally substituted by hydroxy, alkoxy, aryloxy, haloalkoxy, cyano, nitro, mercapto, alkylthio, cycloalkyl, -N(R⁵)₂-C(0)OR⁵, -C(0)N(R⁵)₂ or -N(R⁵)-C(0)-R⁵ where each R⁵ is as defined above.

Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkyl group that the substitution can occur on any carbon of the alkyl group.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above, e.g., methoxy, ethoxy, n-propoxy, 1-methylethoxy (iso-propoxy), n-butoxy, n-pentoxy, 1,1-dimethylethoxy (t-butoxy), and the like. Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkoxy group that the substitution can occur on any carbon of the alkoxy group. The alkyl radical in the alkoxy radical may be optionally substituted as described above.

"Alkylthio" refers to a radical of the formula $-SR_a$ where R_a is an alkyl radical as defined above, e.g., methylthio, ethylthio, n-propylthio, 1-methylethylthio (iso-propylthio), n-butylthio, n-pentylthio, 1,1-dimethylethylthio (t-butylthio), and the like. Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkylthio group that the substitution can occur on any carbon of the alkylthio group. The alkyl radical in the alkylthio radical may be optionally substituted as described above.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to eight carbon atoms, and which is attached to the rest of the molecule by a single bond or a double bond, e.g., ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1, 4-dienyl, and the like. Unless stated otherwise specifically in the specification, the alkenyl radical may be optionally substituted by hydroxy, alkoxy, haloalkoxy, cyano, nitro, mercapto, alkylthio, cycloalkyl, $-N(R^5)_2$, $-C(0)OR^5$, $-C(0)N(R^5)_2$ or $-N(R^5)-C(0)-R^5$ where each R^5 is as defined above. Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkenyl group that the substitution can occur on any carbon of the alkenyl group.

"Alkynyl" refers to a straight or branched monovalent hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl, pent-3-ynyl, and the like. Unless stated otherwise specifically in the specification, the alkynyl radical may be optionally substituted by hydroxy, alkoxy, haloalkoxy, cyano, nitro, mercapto, alkylthio, cycloalkyl, $-N(R^5)_2$, $-C(0)OR^5$, $-C(0)N(R^5)_2$ or $-N(R^5)-C(0)-R^5$ where each R^5 is as defined above. Unless stated otherwise specifically in the specification, it is understood that for radicals, as defined below, that contain a substituted alkynyl group that the substitution can occur on any carbon of the alkynyl group.

"Aryl" refers to a phenyl or naphthyl radical. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents selected from the group consisting of alkyl, halo, nitro, cyano, haloalkyl, haloalkoxy, mercapto, alkylthio, phenyl, cycloalkyl, $-OR^{<5>}$ (including hydroxy and alkoxy), $-N(R^5)_2$, $-R^6-N(R^5)_2$, $-N(R^5)-C(0)OR^5$, $-R^6-N(R^5)-C(0)OR^5$, $-N(R^5)-C(0)-R^5$, $-R^6-N(R^5)-C(0)-R^5$, $-C(0)OR^5$, $-R^6-C(0)OR^5$, $-C(0)-N(R^5)_2$, $-R^6-C(0)-N(R^5)_2$, $-C(0)-$

$R^6-N(R^5)_2$, $-N(R^5)-C(NR^5)-N(R^5)_2$, $-N(R^5)-C(0)-N(R^5)_2$ and $-N(R^5)-C(0)-R^6-N(R^5)_2$ where each R^5 and R^6 are as defined above.

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above and R_b is one or more aryl radicals as defined above, e.g., benzyl, diphenylmethyl and the like. The aryl radical(s) may be optionally substituted as described above.

"Aralkoxy" refers to a radical of the formula $-OR_d$ where R_d is an aralkyl radical as defined above, e.g., benzyloxy, and the like. The aryl radical may be optionally substituted as described above.

"Aralkenyl" refers to a radical of the formula $-R_cR_b$ where R_c is an alkenyl radical as defined above and R_b is one or more aryl radicals as defined above, e.g., 3-phenylprop-1-enyl, and the like. The aryl radical(s) and the alkenyl radical may be optionally substituted as described above.

"Alkylene chain" refers to a straight or branched divalent hydrocarbon chain consisting solely of carbon and hydrogen, containing no unsaturation and having from one to eight carbon atoms, e.g., methylene, ethylene, propylene, n-butylene, and the like. The alkylene chain may be optionally substituted by one or more substituents selected from the group consisting of aryl, halo, hydroxy, alkoxy, haloalkoxy, cyano, nitro, mercapto, alkylthio, cycloalkyl, $-N(R^5)_2$, $-C(0)OR^5$, $-C(0)N(R^5)_2$ or $-N(R^5)-C(0)-R^5$ where each R^5 is as described above. The alkylene chain may be attached to the rest of the molecule through any two carbons within the chain.

"Alkenylene chain" refers to a straight or branched divalent hydrocarbon chain consisting solely of carbon and hydrogen, containing at least one double bond and having from two to eight carbon atoms, e.g., ethenylene, prop-1-enylene, but-1-enylene, pent-1-enylene, hexa-1,4-dienylene, and the like. The alkenylene chain may be optionally substituted by one or more substituents selected from the group consisting of aryl, halo, hydroxy, alkoxy, haloalkoxy, cyano, nitro, mercapto, alkylthio, cycloalkyl, $-N(R^5)_2$, $-C(0)OR^5$, $-C(0)N(R^5)_2$ or $-N(R^5)-C(0)-R^5$ where each R^5 is as described above. The alkenylene chain may be attached to the rest of the molecule through any two carbons within the chain.

"Cycloalkyl" refers to a stable monovalent monocyclic or bicyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from three to ten carbon atoms, and which is saturated and attached to the rest of the molecule by a single bond, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decalinyl and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro, mercapto, alkylthio, cycloalkyl, $-N(R^5)_2$, $-C(0)OR^5$, $-C(0)N(R^5)_2$ or $-N(R^5)-C(0)-R^5$ where each R^5 is as defined above.

"Cycloalkylene" refers to a stable divalent monocyclic or bicyclic hydrocarbon consisting solely of carbon and hydrogen atoms, having from three to ten carbon atoms, and which is saturated and attached to the rest of the molecule by two single bonds, e.g., cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, decalinylenes and the like. Unless otherwise stated specifically in the specification, the term "cycloalkylene" is meant to include cycloalkylene moieties which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, aryl, aralkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro, mercapto, alkylthio, cycloalkyl, $-N(R^5)_2$, $-C(0)OR^5$, $-C(0)N(R^5)_2$ or $-N(R^5)-C(0)-R^5$ where each R^5 is as defined above.

"N-heterocyclyl" refers to a stable 3- to 15-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein at least one of the heteroatoms is a nitrogen. For the purposes of this invention, the N-heterocyclyl radical may be a monocyclic, bicyclic or a tricyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the N-heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the N-heterocyclyl radical may be partially or fully saturated or aromatic. The N-heterocyclyl radical may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such N-heterocyclyl radicals include, but are not limited to, azepinyl, azetidiny, benzimidazolyl, benzoxazolyl, carbazolyl, decahydroisoquinolyl, quinuclidinyl, imidazolyl, imidazoliny, imidazolidinyl, isothiazolidinyl, indolyl, isoindolyl, indoliny, isoindoliny, indoliziny, isoxazolyl, isoxazolidinyl, morpholiny, benzothiadiazolyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, perhydroazepinyl, piperidinyl, piperazinyl, 4-piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinoliny, quinuclidinyl, isoquinoliny, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydroisoquinolyl, thiomorpholiny, thiomorpholiny sulfide, and thiomorpholiny sulfone. The carbon atoms in the N-heterocyclyl radical may be optionally substituted by alkyl, halo, nitro, cyano, haloalkyl, haloalkoxy, mercapto, alkylthio, phenyl, cycloalkyl, $-OR^5$, $-N(R^5)_2$, $-R^6-N(R^5)_2$, $-N(R^5)-C(0)OR^5$, $-R^6-N(R^5)-C(0)OR^5$, $-N(R^5)-C(0)-R^5$, $-R^6-N(R^5)-C(0)-R^5$, $-C(0)OR^5$, $-R^6-C(0)OR^5$, $-C(0)-N(R^5)_2$, $-R^6-C(0)-N(R^5)_2$, $-C(0)-R^6-N(R^5)_2$, $-N(R^5)-C(NR^5)-N(R^5)_2$, $-N(R^5)-C(0)-N(R^5)_2$ and $-N(R^5)-C(0)-R^6-N(R^5)_2$ where each R^5 and R^6 are as defined above.

The nitrogen atoms in the N-heterocyclyl may be optionally substituted by $-C(NR^5)-N(R^5)_2$, $-C(NR^5)-R^6$, $-C(0)-N(R^5)_2$ or $-C(0)-R^5-N(R^5)_2$ where each R^5 and R^6 are as defined above. Preferred N-heterocyclyl radicals are piperidinyl, tetrahydroisoquinoliny, or benzothiadiazolyl.

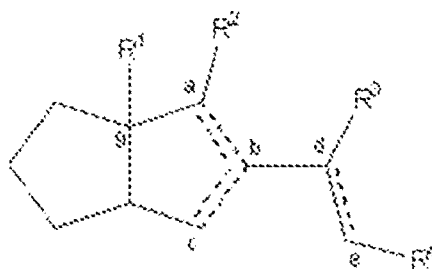
"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like. "Haloalkoxy" refers to a radical of the formula -OR_c where R_c is an haloalkyl radical as defined above, e.g., trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, 1-fluoromethyl-2-fluoroethoxy, 3-bromo-2-fluoropropoxy, 1-bromomethyl-2-bromoethoxy, and the like.

The LRH-1 agonist of the invention can preferably be a physiologically functional derivative of the 9-substituted bicycle [3.3.0] octane derivative such as a substituted cis-bicyclo[3.3.0]-oct-2-ene derivative described herein.

It will also be appreciated by those skilled in the art that the LRH-1 agonist may also be utilized in the form of a pharmaceutically acceptable salt or solvate thereof. The physiologically acceptable salts include conventional salts formed from pharmaceutical acceptable inorganic or organic acids or bases as well as quaternary ammonium acid addition salts. More specific examples of suitable acid salts include hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic, naphthalene-2-sulfonic, benzenesulfonic hydroxynaphthoic, hydroiodic, malic, steric, tannic and the like. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminium, calcium, zinc, N, N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts. References hereinafter to a LRH1 agonist include both compounds and their pharmaceutical acceptable salts and solvates.

A preferred example of a LRH-1 agonists is a 9-substituted bicycle [3.3.0] octane derivative having formula II



Formula II

wherein

R^1 is $-N(R^5)_2$;

R^2 is H, alkyl, halogen, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene or N-heterocyclyl which can be optionally substituted

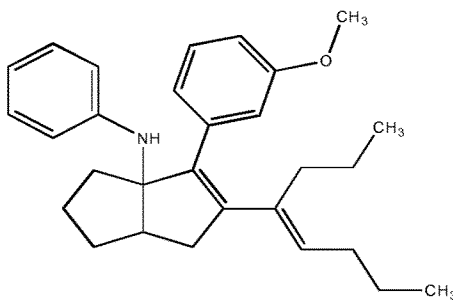
R^3 and R^4 are independently alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene, halogen or N-heterocyclyl;

each R^5 is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl or aralkenyl; and

each R^6 is a straight or branched alkene chain optionally substituted by hydroxy, mercapto, alkylthio, aryl, cycloalkyl, $-N(R^5)_2$, $-C(=O)OR^5$ or $-C(=O)N(R^5)_2$; and

wherein there is independently a maximum of one double bond between each of the carbon atoms of the centers a-b and b-c and d-e.

More preferably, said agonist is a 9-substituted bicyclo [3.3.0] octane derivative (from hereinafter compound "BL001") having formula III



Formula III

or a pharmaceutically acceptable salt thereof.

As used herein, subjects suffering from a disease in need of increasing the secretion of anti-inflammatory cytokines, such as IL-10, in the leukocytes, include those already with the pathologic condition and/or those prone to have the pathologic condition and/or those in whom the disorder is to be prevented. Accordingly, those already with the pathologic condition are treated and thus subject to a treatment with an LRH-1 agonist. However, it is noted that as used herein, the term "prevention", "prophylactic treatment" or "preventing" differs from the term "therapeutic treatment" since "therapeutic treatment" is only understood herein as the therapeutic treatment after the clinical manifestation of the disease. In contrast, the terms "prevention" "prophylactic treatment" or "preventing" refer to the treatment of the disease before its clinical manifestations in those subjects prone to have the pathologic condition and/or in those in whom the disorder is to be prevented.

A subject is successfully "therapeutically treated" if, after receiving an amount of an LRH-1 agonist according to the teaching of the invention, the subject shows a detectable, observable

and/or measurable reversion of the clinical manifestations of the disease. The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in a detectable and/or measurable reversion of the clinical manifestations of the disease. The exact dose will depend on the purpose of the prevention/therapeutic treatment, and will be ascertainable by one skilled in the art using known techniques. As is known in the art, adjustments for age, body weight, general health, sex, diet, drug interaction and the severity of the pathological condition may be necessary, and will be ascertainable with routine experimentation by those skilled in the art. The therapeutic effect of the LRH-1 agonist of the invention is additionally detectable by all established methods and approaches which will indicate a therapeutic effect.

As already stated the present invention relates to compounds, compositions and methods which can be used for the treatment of cancer or inflammation. In particular, the present invention relates to LRH-1 agonists as defined in the specification, for use in a method of increasing the secretion of anti-inflammatory cytokines, such as IL-10, in the leukocytes of a subject in need thereof suffering from cancer or an inflammatory disease or condition.

Several cytokines with inflammatory effects have been described. Preferably, the LRH-1 agonist or pharmaceutically acceptable salt thereof for use in the method of the invention is capable of increasing the secretion of anti-inflammatory cytokines selected from the group consisting of IL-10, IL-4, IL-5 and IL-6, more preferably said anti-inflammatory cytokines are IL-10 and/or IL-4.

The secretion of said anti-inflammatory cytokines has been associated by the inventors with an increase of immune cells with an anti-inflammatory profile such as T regulatory cells (CD4/CD25/FoxP3+ T regs), T helper cells of the Th2 subtype or activated macrophages of the M2 subtype. More specifically, as described in Example 1 the inventors have found that increases in IL10, IL5 and to a lesser extent IL6 induced by the LRH-1 agonist of the invention results in a shift towards a greater number of anti-inflammatory immune cells such as Tregs and Th2. Moreover, it was described by the inventors that the secretion of IL10 promoted by the LRH-1 agonist of the invention also induces M2 macrophage maturation, leading to a further secretion of IL10 and IL4.

In a particular embodiment, the invention refers to a LRH-1 agonist according to the invention or a pharmaceutically acceptable salt thereof for use in a method of treating a subject in need thereof suffering from cancer or an inflammatory disease or condition, wherein said LRH-1 agonist according to the invention or pharmaceutically acceptable salt thereof is capable of increasing the number of immune cells with an anti-inflammatory profile, preferably wherein said cells are selected from the group consisting of T regs, Th2 cells and M2 macrophages.

Diseases and disorders which have significant inflammatory components are ubiquitous. Skin disorders, bowel disorders, certain degenerative neurological disorders, arthritis, autoimmune diseases and other illnesses afflict many patients. The factors underlying these disorders are varied and include infectious agents, autoimmune factors, dietary or environmental factors and genetic factors. In the majority of cases, the causative elements have not been defined and many of the key pathophysiological components have not been elucidated. Accordingly, treatment options for the majority of these diseases is suboptimal.

While reducing the present invention to practice, the present inventor uncovered that subjects suffering from inflammatory disease can treat such diseases by altering the cytokine profile produced by leukocytes from pro-inflammatory cytokines to anti-inflammatory cytokines. These findings suggest, for the first time, that LHR-1 is a novel target for treatment of inflammatory diseases.

A number of diseases and conditions, which typically cause inflammatory response in individuals can be treated using the methodology described hereinabove.

Examples of such diseases and conditions are summarized infra.

Inflammatory diseases include, but are not limited to, chronic inflammatory diseases and acute inflammatory diseases.

Inflammatory diseases associated with hypersensitivity. Examples of hypersensitivity include, but are not limited to, Type I hypersensitivity, Type II hypersensitivity, Type III hypersensitivity, Type IV hypersensitivity, immediate hypersensitivity, antibody mediated hypersensitivity, immune complex mediated hypersensitivity, T lymphocyte mediated hypersensitivity and DTH.

Type I or immediate hypersensitivity, such as asthma.

Type II hypersensitivity include, but are not limited to, rheumatoid diseases, rheumatoid autoimmune diseases, rheumatoid arthritis (Krenn V. et al., *Histol Histopathol* 2000 Ju1 ; 15 (3): 791), spondylitis, ankylosing spondylitis (Jan Voswinkel et al., *Arthritis Res* 2001; 3 (3): 189), systemic diseases, systemic autoimmune diseases, systemic lupus erythematosus (Erikson J. et al., *Immunol Res* 1998; 17 (1-2): 49), sclerosis, systemic sclerosis (Renaudineau Y. et al., *Clin Diagn Lab Immunol.* 1999 Mar ; 6 (2): 156); Chan OT. et al., *Immunol Rev* 1999 Jun; 169: 107), glandular diseases, glandular autoimmune diseases, pancreatic autoimmune diseases, diabetes, Type I diabetes (Zimmet P. *Diabetes Res Clin Pract* 1996 Oct; 34 Suppl: S125), thyroid diseases, autoimmune thyroid diseases, Graves'disease (Orgiazzi J. *Endocrinol Metab Clin North Am* 2000 Jun ; 29 (2): 339), thyroiditis, spontaneous autoimmune thyroiditis (Braley-Mullen H. and Yu S, *J Immunol* 2000 Dec 15; 165 (12): 7262), Hashimoto's thyroiditis (Toyoda N. et al., *Nippon Rinsho* 1999 Aug; 57 (8): 1810), myxedema, idiopathic myxedema (Mitsuma T. *Nippon Rinsho.* 1999 Aug; 57 (8): 1759); autoimmune reproductive diseases, ovarian diseases, ovarian autoimmunity (Garza KM. et al., *J Reprod Immunol* 1998 Feb; 37 (2): 87), autoimmune

anti-sperm infertility (Diekman AB. et al., Am J Reprod Immunol. 2000 Mar ; 43 (3): 134), repeated fetal loss (Tincani A. et al., Lupus 1998; 7 Suppl 2: S107-9), neurodegenerative diseases, neurological diseases, neurological autoimmune diseases, multiple sclerosis (Cross AH. et al., J Neuroimmunol 2001 Jan 1 ; 112 (1-2): 1), Alzheimer's disease (Oron L. et al., J Neural Transm Suppl. 1997; 49: 77), myasthenia gravis (Infante AJ. And Kraig E, Int Rev Immunol 1999 ; 18 (1-2): 83), motor neuropathies (Kornberg AJ. J Clin Neurosci. 2000 May ; 7 (3): 191), Guillain-Barre syndrome, neuropathies and autoimmune neuropathies (Kusunoki S. Am J Med Sci. 2000 Apr; 319 (4): 234), myasthenic diseases, Lambert-Eaton myasthenic syndrome (Takamori M. Am J Med Sci. 2000 Apr; 319 (4): 204), paraneoplastic neurological diseases, cerebellar atrophy, paraneoplastic cerebellar atrophy, non-paraneoplastic stiff man syndrome, cerebellar atrophies, progressive cerebellar atrophies, encephalitis, Rasmussen's encephalitis, amyotrophic lateral sclerosis, Sydeham chorea, Gilles de la Tourette syndrome, polyendocrinopathies, autoimmune polyendocrinopathies (Antoine JC. and Honnorat J. Rev Neurol (Paris) 2000 Jan; 156 (1): 23); neuropathies, dysimmune neuropathies (Nobile-Orazio E. et al., Electroencephalogr Clin Neurophysiol Suppl 1999; 50: 419); neuromyotonia, acquired neuromyotonia, arthrogryposis multiplex congenita (Vincent A. et al., Ann N Y Acad Sci. 1998 May 13; 841: 482), cardiovascular diseases, cardiovascular autoimmune diseases, atherosclerosis (Matsuura E. et al., Lupus. 1998 ; 7 Suppl 2: S135), myocardial infarction (Vaarala O. Lupus. 1998 ; 7 Suppl 2: S132), thrombosis (Tincani A. et al., Lupus 1998 ; 7 Suppl 2: S107-9), granulomatosis, Wegener's granulomatosis, arteritis, Takayasu's arteritis and Kawasaki syndrome (Praprotnik S. et al., Wien Klin Wochenschr 2000 Aug 25 ; 112 (15-16) : 660); anti-factor VIII autoimmune disease (Lacroix-Desmazes S. et al., Semin Thromb Hemost. 2000; 26 (2): 157); vasculitises, necrotizing small vessel vasculitises, microscopic polyangiitis, Churg and Strauss syndrome, glomerulonephritis, pauci-immune focal necrotizing glomerulonephritis, crescentic glomerulonephritis (Noel LH. Ann Med Interne (Paris). 2000 May ; 151 (3) : 178) ; antiphospholipid syndrome (Flamholz R. et al., J Clin Apheresis 1999 ; 14 (4) : 171); heart failure, agonist-like p-adrenoceptor antibodies in heart failure (Wallukat G. et al., Am J Cardiol. 1999 Jun 17 ; 83 (12A): 75H), thrombocytopenic purpura (Moccia F. Ann Ital Med Int. 1999 Apr-Jun; 14 (2): 114); hemolytic anemia, autoimmune hemolytic anemia (Efremov DG. et al., Leuk Lymphoma 1998 Jan; 28 (3-4): 285), gastrointestinal diseases, autoimmune diseases of the gastrointestinal tract, intestinal diseases, chronic inflammatory intestinal disease (Garcia Herola A. et al., Gastroenterol Hepatol. 2000 Jan; 23 (1) : 16), celiac disease (Landau YE. and Shoenfeld Y. Harefuah 2000 Jan 16; 138 (2): 122), autoimmune diseases of the musculature, myositis, autoimmune myositis, Sjogren's syndrome (Feist E. et al., Int Arch Allergy Immunol 2000 Sep; 123 (1) : 92); smooth muscle autoimmune disease (Zauli D. et al., Biomed Pharmacother 1999 Jun; 53 (5-6) 234), hepatic diseases, hepatic autoimmune diseases,

autoimmune hepatitis (Manns MP. *J Hepatol* 2000 Aug; 33 (2): 326) and primary biliary cirrhosis (Strassburg CP. et al., *Eur J Gastroenterol Hepatol*. 1999 Jun; 11 (6): 595).

Type IV or T cell mediated hypersensitivity, include, but are not limited to, rheumatoid diseases, rheumatoid arthritis (Tisch R, McDevitt HO. *Proc Natl Acad Sci U S A* 1994 Jan 18; 91 (2): 437), systemic diseases, systemic autoimmune diseases, systemic lupus erythematosus (Datta SK. , *Lupus* 1998; 7 (9): 591), glandular diseases, glandular autoimmune diseases, pancreatic diseases, pancreatic autoimmune diseases, Type 1 diabetes (Castano L. and Eisenbarth GS. *Ann. Rev. Immunol.* 8: 647); thyroid diseases, autoimmune thyroid diseases, Graves'disease (Sakata S. et al., *Mol Cell Endocrinol* 1993 Mar; 92 (1): 77); ovarian diseases (Garza KM. et al., *J Reprod Immunol* 1998 Feb; 37 (2): 87), prostatitis, autoimmune prostatitis (Alexander RB. et al., *Urology* 1997 Dec; 50 (6): 893), polyglandular syndrome, autoimmune polyglandular syndrome, Type I autoimmune polyglandular syndrome (Hara T. et al., *Blood*. 1991 Mar 1; 77 (5): 1127), neurological diseases, autoimmune neurological diseases, multiple sclerosis, neuritis, optic neuritis (Soderstrom M. et al., *J Neurol Neurosurg Psychiatry* 1994 May ; 57 (5): 544), myasthenia gravis (Oshima M. et al., *Eur J Immunol* 1990 Dec ; 20 (12): 2563), stiff-man syndrome (Hiemstra HS. et al., *Proc Natl Acad Sci U S A* 2001 Mar 27; 98 (7): 3988), cardiovascular diseases, cardiac autoimmunity in Chagas'disease (Cunha-Neto E. et al., *J Clin Invest* 1996 Oct 15; 98 (8) : 1709), autoimmune thrombocytopenic purpura (Semple JW. et al., *Blood* 1996 May 15987 (IOJ : 4945), anti- helper T lymphocyte autoimmunity (Caporossi AP. et al., *Viral Immunol* 1998 ; 11 (1) : 9), hemolytic anemia (Sallah S. et al., *Ann Hematol* 1997 Mar; 74 (3): 139), hepatic diseases, hepatic autoimmune diseases, hepatitis, chronic active hepatitis (Franco A. et al., *Clin Immunol Immunopathol* 1990 Mar; 54 (3): 382), biliary cirrhosis, primary biliary cirrhosis (Jones DE. *Clin Sci (Colch)* 1996 Nov; 91 (5): 551), nephric diseases, nephric autoimmune diseases, nephritis, interstitial nephritis (Kelly CJ. *J Am Soc Nephrol* 1990 Aug; 1 (2): 140), connective tissue diseases, ear diseases, autoimmune connective tissue diseases, autoimmune ear disease (Yoo TJ. et al., *Cell Immunol* 1994 Aug; 157 (1): 249), disease of the inner ear (Gloddek B. et al., *Ann N Y Acad Sci* 1997 Dec 29 ; 830: 266), skin diseases, cutaneous diseases, dermal diseases, bullous skin diseases, pemphigus vulgaris, bullous pemphigoid and pemphigus foliaceus.

Examples of delayed type hypersensitivity include, but are not limited to, contact dermatitis and drug eruption.

Examples of types of T lymphocyte mediating hypersensitivity include, but are not limited to, helper T lymphocytes and cytotoxic T lymphocytes.

Examples of helper T lymphocyte-mediated hypersensitivity include, but are not limited to, Th1 lymphocyte mediated hypersensitivity and Th2 lymphocyte mediated hypersensitivity. The methods of the present invention can also be used for the therapeutic or prophylactic treatment of autoimmune diseases selected, but not limited, to the following list: Acute

Disseminated Encephalomyelitis (ADEM); Acute necrotizing hemorrhagic leukoencephalitis; Addison's disease; Agammaglobulinemia; Alopecia areata; Amyloidosis; Ankylosing spondylitis; Anti-GBM/Anti-TBM nephritis; Antiphospholipid syndrome (APS); Autoimmune angioedema; Autoimmune aplastic anemia; Autoimmune dysautonomia; Autoimmune hepatitis; Autoimmune hyperlipidemia; Autoimmune immunodeficiency; Autoimmune inner ear disease (AIED); Autoimmune myocarditis; Autoimmune oophoritis; Autoimmune pancreatitis; Autoimmune retinopathy; Autoimmune thrombocytopenic purpura (ATP); Autoimmune thyroid disease; Autoimmune urticarial; Axonal & neuronal neuropathies; Balo disease; Behcet's disease; Bullous pemphigoid; Cardiomyopathy; Castleman disease; Celiac disease; Chagas disease; Chronic fatigue syndrome; Chronic inflammatory demyelinating polyneuropathy (CIDP) ; Chronic recurrent multifocal osteomyelitis (CRMO); Churg-Strauss syndrome; Cicatricial pemphigoid/benign mucosal pemphigoid; Crohn's disease; Cogan's syndrome; Cold agglutinin disease; Congenital heart block; Coxsackie myocarditis; CREST disease; Essential mixed cryoglobulinemia; Demyelinating neuropathies; Dermatitis herpetiformis; Dermatomyositis; Devic's disease (neuromyelitis optica) ; Discoid lupus; Dressler's syndrome; Endometriosis; Eosinophilic esophagitis; Eosinophilic fasciitis; Erythema nodosum; Experimental allergic encephalomyelitis; Evans syndrome; Fibromyalgia; Fibrosing alveolitis; Giant cell arteritis (temporal arteritis); Giant cell myocarditis; Glomerulonephritis; Goodpasture's syndrome; Granulomatosis with Polyangiitis (GPA) (formerly called Wegener's Granulomatosis); Graves' disease; Guillain-Barre syndrome; Hashimoto's encephalitis; Hashimoto's thyroiditis; Hemolytic anemia; Henoch-Schönlein purpura; Herpes gestationis; Hypogammaglobulinemia; Idiopathic thrombocytopenic purpura (ITP); IgA nephropathy; IgG4-related sclerosing disease; Immunoregulatory lipoproteins; Inclusion body myositis; Interstitial cystitis; Juvenile arthritis; Juvenile myositis; Kawasaki syndrome; Lambert-Eaton syndrome; Leukocytoclastic vasculitis; Lichen planus; Lichen sclerosus; Ligneous conjunctivitis; Linear IgA disease (LAD); Lupus (SLE); Lyme disease, chronic; Meniere's disease; Microscopic polyangiitis; Mixed connective tissue disease (MCTD); Mooren's ulcer; Mucha-Habermann disease; Multiple sclerosis; Myasthenia gravis; Myositis; Narcolepsy; Neuromyelitis optica (Devic's); Neutropenia; Ocular cicatricial pemphigoid; Optic neuritis; Palindromic rheumatism; PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus); Paraneoplastic cerebellar degeneration; Paroxysmal nocturnal hemoglobinuria (PNH); Parry Romberg syndrome; Parsonage-Turner syndrome; Pars planitis (peripheral uveitis); Pemphigus; Peripheral neuropathy; Perivenous encephalomyelitis; Pernicious anemia; POEMS syndrome; Polyarteritis nodosa; Type I, II, & III autoimmune polyglandular syndromes; Polymyalgia rheumatica; Polymyositis; Postmyocardial infarction syndrome; Postpericardiotomy syndrome; Progesterone dermatitis; Primary biliary cirrhosis; Primary sclerosing cholangitis; Psoriasis; Psoriatic arthritis; Idiopathic pulmonary fibrosis; Pyoderma gangrenosum; Pure red cell aplasia; Raynaud's phenomenon; Reactive Arthritis; Reflex sympathetic dystrophy; Reiter's syndrome; Relapsing

polychondritis; Restless legs syndrome; Retroperitoneal fibrosis; Rheumatic fever; Rheumatoid arthritis; Sarcoidosis; Schmidt syndrome; Scleritis; Scleroderma; Sjogren's syndrome; Sperm & testicular autoimmunity; Stiff person syndrome; Subacute bacterial endocarditis (SBE); Susac's syndrome; Sympathetic ophthalmia; Takayasu's arteritis; Temporal arteritis/Giant cell arteritis; Thrombocytopenic purpura (TTP); Tolosa-Hunt syndrome; Transverse myelitis; Ulcerative colitis; Undifferentiated connective tissue disease (UCTD); Uveitis; Vasculitis; Vesiculobullous dermatosis; Vitiligo; Wegener's granulomatosis (now termed Granulomatosis with Polyangiitis (GPA)).

The methods of the present invention can also be used for the therapeutic or prophylactic treatment of graft rejection diseases. Examples of diseases associated with transplantation of a graft include, but are not limited to, graft rejection, chronic graft rejection, subacute graft rejection, hyperacute graft rejection, acute graft rejection and graft versus host disease.

The methods of the present invention can also be used for the therapeutic or prophylactic treatment of allergic diseases. Examples of allergic diseases include, but are not limited to, asthma, hives, urticaria, pollen allergy, dust mite allergy, venom allergy, cosmetics allergy, latex allergy, chemical allergy, drug allergy, insect bite allergy, animal dander allergy, stinging plant allergy, poison ivy allergy and food allergy.

IL-10 has also been described to have anti-tumor properties (Berman et al., J Immunol. 1996, 157: 231-8). Functional mechanisms investigated include activation of natural killer (NK) cells (Zheng et al., The Journal of experimental medicine 1996, 184:579-84) that have been associated with tumor clearance in murine models of breast and colorectal cancer (Toiyama et al., Surg Today. 2010, 40:46-53); inhibition of angiogenesis; enhancement of macrophage infiltration into tumors (Richter et al., Cancer Res. 1993, 53:4134-7); and prevention of metastasis by inhibition of matrix metalloproteinase-2 (Stearns et al., Clinical cancer research 2003, 9:1191-9). Moreover, there is currently an on-going clinical trial to evaluate the safety and tolerability of PEGylated recombinant human Interleukin-10 (PEG-rHUIL-10) for its use in the treatment of advanced solid tumors, alone and in combination with other drugs (<https://clinicaltrials.gov/show/NCT02009449>)

Accordingly, the present invention also relates to compounds, compositions and methods which can be used for the treatment of cancer. In particular, the present invention relates to a LRH-1 agonist or a pharmaceutically acceptable salt thereof as defined in the specification, for use in a method of increasing the secretion of anti-inflammatory cytokines, such as IL-10, in the leukocytes of a subject in need thereof suffering from cancer.

The term cancer as used herein is meant to include tumors, neoplasias, and any other malignant disease having as cause malignant tissue or cells. There are several types of cancer. A complete list of cancer types can be found in the website of the National Cancer Institute (NCI): <http://www.cancer.gov/types>. The *international classification of diseases for oncology (ICD-O)* published by the World Health Organization (WHO) provides internationally recognized histopathological and clinical diagnostic criteria (Fritz A et al (eds), 2000, ICD-O International classification of diseases for oncology. World Health Organization, Geneva).

Cancers are typically classified in two ways: by the type of tissue in which the cancer originates (histological type) and by primary site, or the location in the body where the cancer first developed. From a histological standpoint there are many different cancers, which are grouped by the NCI into carcinoma, sarcoma, myeloma, leukemia, lymphoma, and mixed types (a cancer composed by cells of different histological origins, such as adenosquamous carcinoma, mixed mesodermal tumor, carcinosarcoma and teratocarcinoma).

The cancer to be treated may be any type of cancer. In a particular embodiment, said cancer is a solid tumor. The term "solid tumor" does not include an hematologic cancer. The term "hematologic cancer" as used herein refers to leukemia, lymphoma, and multiple myeloma.

Different types of solid tumors are named by the type of cells that form them. Examples of solid tumors are lung cancer, sarcoma, malignant melanoma, mesothelioma, bladder carcinoma, prostate cancer, pancreas carcinoma, gastric carcinoma, ovarian cancer, hepatoma, breast cancer, colorectal cancer, kidney cancer, esophageal cancer, suprarenal cancer, parotid gland cancer, head and neck carcinoma, cervix cancer, mesothelioma and lymphoma. Preferably, said solid tumor is pancreatic carcinoma.

Lastly, as shown in the examples of the present invention, the methods of the present invention are particularly suitable for preventing and/or reverting the development of Type I Diabetes Mellitus and astonishingly for the therapeutic treatment of type II diabetes by, among other effects, improving glucose tolerance in subjects in need thereof.

Consequently, the herein described LRH-1 agonists can be used/applied in methods of the invention by administering a pharmaceutically effectively amount of an LRH-1 agonist described herein to a subject in need thereof. Likewise, the herein described LRH-1 agonists can also be used for the preparation of a medicament/pharmaceutical composition for preventing, ameliorating and/or treating the (medical) conditions as described herein.

The following examples merely illustrate the present invention and do not limit the same.

Examples

Materials and Methods

BL001 synthesis and administration formulation: Large-scale synthesis of the LRH-1 agonist BL001 was outsourced to SreeniLabs (India). The optimal formulation for the administrating of BL001 was found to include Wellsolve (Celeste Corporation, Japan), a solubilizing agent that was shown to significantly increased absorption of poorly water-soluble drugs.

Mice: RIP-B7.1 mice (kindly provided by Prof. B. Boehm, Ulm University Germany) or C57bl/6 mice (purchased from Janvier Labs, France) were housed in ventilated plastic cages under a 12-hour light/dark cycle and were given food as well as water *ad libidum*. Mice experimentations were approved by the CABIMER Animal Committee and performed in accordance with the Spanish law on animal use RD 53/2013.

Mice treatment: Seven or 8 week-old RIP-B7.1 mice were treated with BL001 (10 mg/kg body weight intraperitoneally once daily) either 5 days prior or post immunization. Immunization to induce autoimmune diabetes was achieved by intramuscular injection of 50 ug of a preproinsulin (ppINS) expression plasmid (PlasmidFactory GmbH, Germany) into both anterior tibialis muscle. Mice were sacrificed at 4, 6 and 8 weeks post-immunization and pancreases as well as spleens were extracted for immunocytochemistry analysis and proliferation assay, respectively. In addition, 8-week-old C57bl/6 were treated with BL001 for 5 days and then injected intraperitoneally with streptozotocin (STZ, 150 mg STZ/kg body weight prepared in 0.1mM sodium citrate at pH 4.5). Alternatively, 8 week-old C57bl/6 mice were given a high fat diet (HFD) for 12 weeks. Administration of BL001 was initiated 8 weeks into the HFD treatment.

Glucose measurements: Blood was collected from tail vein and glucose levels were measured with an Optium Xceed glucometer (Abbott Scientifica SA, Spain). In instances in which glucose tolerance tests (GTT) were performed, animals were initially fasted overnight and then injected intraperitoneally with 2g glucose/kg body weight (BW).

Blood cytokine profiling: Blood samples (20 ul) were collected prior to sacrifice at 8 weeks from various experimental groups. Cytokine levels were simultaneously assessed using the mouse V-PLEX ProInflammatory Panel 1 kit 10-Plex from Meso Scale Discovery (MSD). Detection was performed using proprietary electrochemiluminescence technology and data acquired on a MESOTM QuickPlex SQ120 (MSD).

Splenocyte proliferation assay: Splenocytes were initially isolated from spleens and subjected to a proliferation assay. To this end, splenocytes were cultured in the presence of an antigenic insulin peptide fragment (SLYQLENYCA) for 72 hours. Cells were pulsed with [³H]-thymidine for the last 24 hours of culture and harvested onto membranes, and proliferation was determined by measuring [³H]-thymidine incorporation.

Flow cytometry: The following monoclonal antibodies were used to isolate subpopulations of T helper cells from mouse pancreas extracts using flow cytometry (FACSCalibur, Becton, Dickinson and Company,): FITC-conjugated anti-mouse CD4 antibody for labeling (entire Th cell subpopulation) combined with Alexa fluor 647-conjugated anti-mouse IL17 (Th17), Alexa fluor 647-conjugated anti-mouse IL4 (Th2) or PE-Cy7-conjugated anti-mouse IFN γ . The following monoclonal antibodies were used to isolate subpopulations of T helper cells from mouse pancreas extracts using flow cytometry (FACSCalibur, Becton, Dickinson and Company).

Histology and immunohistochemistry. Pancreases were dissected and fixed in 4% paraformaldehyde. Dehydration, embedding and sectioning were performed at the CABIMER Histology platform. Sections were rehydrated in ethanol and blocked in PBS containing 1% BSA and 0,1% Tween. Hematoxylin and eosin (H&E) staining was used to assess insulinitis. For immunofluorescence analysis, the following primary polyclonal antibodies were used: Rabbit anti-insulin (Santa Cruz) and mouse anti-glucagon (Sigma-Aldrich). The following secondary antibodies were added: Alexa Fluor 488 goat anti-mouse (Life Technologies) and Alexa Fluor 568 goat anti-rabbit (Life Technologies). Nuclear counterstaining was performed by DAPI staining and sections were mounted using DAKO fluorescent mounting medium. Lymphocytic infiltration (insulinitis) was scored based on H&E staining of islet paraffin sections. Insulinitis scores were determined as follows: 0, no infiltration, 1, minimal focal infiltration, 2, peri-islet infiltration, 4, extensive infiltration. Results are presented as percent of total islets counted for all groups.

Cell culture, treatment and cytokine measurement. The murine RAW264.7 macrophage cell line was cultured in DMEM supplemented with 2mM L-glutamine, 100U/ml penicillin, 100 g/ml streptomycin and 10% FBS. Cells were grown and maintained at 37 C in a humidified incubator with 5% CO₂. Cells were stimulated with increasing amounts of LPS (0.25, 0.5 and 1 ug/ml in DMSO) in the absence or presence of increasing concentrations of BL001 (0.1, 1 and 10 uM) for 24 hours. Cell viability and proliferation were assessed using the MTT assay and BrdU incorporation. Cytokines secretion to the medium was measured by electrochemiluminescence (ECL) technology from MesoScale Discovery (MSD).

Statistical analysis. Results are expressed as mean $\pm$ SEM. Statistical differences were estimated using the: unpaired t test, ANOVA with Bonferroni post hoc test or non-parametric Mann-Whitney test (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Example 1. BL001 prevents and reverts the development of Type 1 Diabetes Mellitus

Using the RIP-B7.1 mouse model of experimental autoimmune diabetes we herein demonstrate that pre-treatment of BL001 prior to induction of the autoimmune attack by immunization reduces by 50% the incidence of hyperglycaemia (see Figure 1). In addition, histological analysis and quantification of lymphocyte infiltration (insulitis) performed on pancreas sections of animals sacrificed at 8 weeks post-treatment revealed massive insulitis in immunized and vehicle treated RIPB7.1 that developed hyperglycemia whereas normoglycemic BL001 treated and immunized animals revealed marginal to no insulitis (see Figure 2A and Figure 7B). Unexpectedly, immunized and BL001 treated mice displayed a similarly high degree of insulitis as compared to immunized animals 4 weeks post treatment (Figure 7A) suggesting that BL001 does not prevent the initial autoimmune response but rather inhibits progression. Immunohistochemical analysis of insulin and glucagon confirmed the complete destruction of β -cells in islets of vehicle-treated animals 8-weeks post immunization. Islet architecture comprising β -cells in the core and α -cells at the periphery of the microorgan was completely preserved in BL001 and immunized mice that remained normoglycemic, similar to that of vehicle or BL001 non-immunized RIP-B7.1 mice (see Figure 2B).

The temporal rescindment of insulitis in immunized and BL001-treated animals suggests that the LRH1 agonist favours an anti-inflammatory environment. Consistent with this premise significantly higher levels of IL10 and IL5 levels were measured in BL001-treated and immunized RIP-B7.1 mice as compared to control immunized animals (see Figure 7C and D). Although non-significant, IL6 levels were slightly higher in BL001-treated and immunized RIP-B7.1 mice as compared to immunized animals (see Figure 7E). The anti-inflammatory cytokine IL10 is predominantly secreted by CD4/CD25/FoxP3⁺ Tregs (Tregs) that possess potent immunosuppressive properties. Furthermore, increased circulating levels of IL5 have been associated with a shift in the T helper (Th) cell population from the pro-inflammatory Th1 subset towards the anti-inflammatory Th2 subset. Similarly, IL6 was shown to promote differentiation of Th2 cells and inhibits the differentiation of Th1 subpopulation. Of particular importance is the finding that higher levels of circulating Th2 cells were associated with diabetes protection. Accordingly, flow cytometry revealed a significant increase in the proportion of pancreatic Tregs in BL001-treated and immunized RIP-B7.1 mice as compared to control animals (see Figure 8A). Although, this proportion was lower in immunized non BL001-treated animals, the latter did not reach statistical significance as compared to BL001 treated and immunized mice (see

Figure 8A). In parallel, a significant increase in Th2 cells with a concomitant decrease in Th1 cells was detected in immunized and BL001-treated animals (see Figure 8B-C). Interestingly the related type 1 diabetes Th17 cell subpopulation was not altered by BL001 (see Figure 8D).

Our findings suggest that BL001-mediated increases in IL10, IL5 and to a lesser extent IL6 reflects a shift towards a greater number of anti-inflammatory immune cells such as Tregs and Th2 that will collectively alter the course of experimental autoimmune diabetes in the RIP-B7.1 mice. Interestingly, Tregs that secrete IL10 were also shown to promote polarization of macrophage towards the anti-inflammatory M2 phenotype to the detriment of the pro-inflammatory M1 subtype. Activated M2 cells will in turn produce higher levels of the anti-inflammatory cytokines IL10 as well as IL-4 that will further stimulate proliferation of Th2 cells. To address whether BL001 could directly promote the M2 subtype we took advantage of the mouse macrophage cell line Raw 264.7 that upon exposure to lipopolysaccharide (LPS) is activated towards the M1 phenotype leading to the secretion of inflammatory cytokines. The rationale was to determine whether BL001 treatment could favour secretion of anti-inflammatory cytokines such IL10 and IL4. BL001 with or without LPS did not alter cell viability (see Figure 5A). Consistent with activation and maturation of RAW264.7 cells, LPS treatment inhibited cell proliferation (see Figure 5B) with a concomitant increase in cytokines secretion (see Figure 5C and Figure 9). However, BL001 in the presence of increasing amounts of LPS dose dependently stimulated secretion of the anti-inflammatory cytokines IL-10 and IL4 without altering release of $\text{TNF}\alpha$ and IL-2 (see Figure 5C and Figure 9A-C). Interestingly, IL-1 β was also enhanced at low LPS concentrations (see Figure 5C).

Thus, in addition to stimulate Tregs and Th2 expansion, BL001 also promotes M2 macrophage maturation leading to further secretion of IL10 and IL4 that all together will orchestrate re-establishment of peripheral tolerance and immune homeostasis (see Figure 10)

Having established that BL001 can prevent, reduce and/ or block the development of hyperglycaemia prior to the induction of experimental autoimmune diabetes partly through modulation of immune cells, we next assessed the capacity of BL001 to revert progression of an ongoing autoimmune attack, a pathological condition reflecting the reality of type 1 diabetic patients (see Figure 3A). Interestingly, the incidence of hyperglycaemia was identical in vehicle- and BL001-treated animals for the initial 4-weeks post immunization indicating a comparable autoimmune attack evolution in both groups (see Figure 3B). However, the incidence of hyperglycaemia was gradually dampened to approximately 30 to 35% in BL001-treated animals while the incidence continued to escalate in vehicle-treated mice reaching 75% by week 8 (see Figure 3B).

In order to confirm that normoglycemic BL001-treated RIP-B7.1 mice mounted an autoimmune attack subsequent to immunization, we performed a splenocyte proliferation assay to

demonstrate the presence of autoreactive T-cells. As expected, an increase in proliferation of splenocytes derived from immunized non-BL001 treated and hyperglycaemic animals was detected upon exposure to the insulin antigenic peptide as compared to control splenocytes (see Figure 4). More remarkably, a similar increase was also observed in BL001-treated and immunized animals confirming that these animals mounted an immune response against β -cells yet did not develop hyperglycaemia (see Figure 4).

The present findings indicate that BL001 in addition to act as a β -cell pro-survival factor also acts as an immunomodulator directly suppressing local inflammation by promoting an anti-inflammatory response characterized by an increase in Tregs, Th2 and M2 macrophages combined with higher levels of IL10 and IL4 (see Figure 10). The latter is highly relevant as to date no pharmacological compounds that either improve β -cell viability or suppress insulinitis are available for the treatment of Type 1 diabetes mellitus. A compound acting at the interface between β -cells and immunity represents a major advancement for the treatment of Type 1 diabetes mellitus. Indeed, the sole and life depending treatment for patients inflicted with this disease is insulin injection that merely attempts to controls blood glucose levels. This treatment is not intended to eradicate disease root.

Thus agonists of LRH-1 address directly this gap for the treatment of Type 1 diabetes mellitus as well as other autoimmune diseases.

Example 2. BL001-treatment improves glucose tolerance in mice fed a high fat diet.

Recent evidence suggests that obesity is associated with inflammation and that the pathogenesis of Type 2 Diabetes Mellitus can be viewed as an auto inflammatory disease. We thus assessed whether BL001 could improve hyperglycaemia in an animal model of high fat diet (HFD)-induced obesity. (see Figure 6A). As illustrated in Figure 6B, BL001-treatment improves glucose tolerance in mice fed a HFD.

Consequently, agonists of LRH-1 improve glucose tolerance and are thus useful for the treatment of Type 2 Diabetes Mellitus.

Example 3. BL001-treatment prevents streptozotocin (STZ)-induced hyperglycaemia in mice.

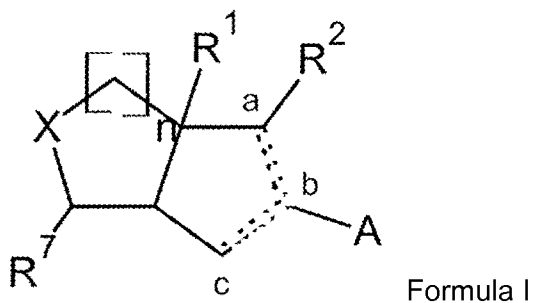
Streptozotocin is a chemical compound that is selectively taken up by β -cells through the glucose transporter 2 (Glut2) that upon degradation will generate reactive oxygen species causing DNA damage and activation of the inflammasome ultimately leading to cell death from which ensues hyperglycaemia. Thus, STZ chemically recapitulates inflammation conditions observed in Type 1 and type 2 diabetes. To assess the protective role of BL001, mice treated or not with the agonist were challenged with a single high dose of STZ to destroy β -cells. Control

STZ-injected mice rapidly developed hyperglycaemia while BL001 treated mice remained normoglycemic (Figure 11A). Four-weeks post STZ injection, 100% of control animal were hyperglycaemic while only 20% of BL001-treated animals exhibited high glucose levels (Figure 11B).

Consequently, agonists of LRH-1 prevents development of hyperglycaemia by protecting islet beta cells against apoptosis in the face of a chemical stress mimicking conditions observed in both type 1 and type 2 diabetes.

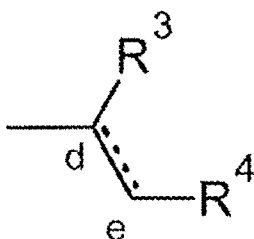
Claims

1. A LRH-1 agonist, wherein said agonist is a 9-substituted bicycle [3.3.0] octane derivative of the following formula



wherein

A is methyl, ethyl, aryl, cycloalkyl or



X is C(R)₂ or NR;

n is 1 or 2;

R is H, alkyl or R is OR¹⁰ wherein R¹⁰ is H, alkyl, acyl;

R¹ is -N(R⁵)₂, OR¹¹ or C(R¹²)=CH₂;

R² is H, alkyl, halogen, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene or N-heterocyclyl which can be optionally substituted;

R³ and R⁴ are independently H, alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene, halogen or N-heterocyclyl;

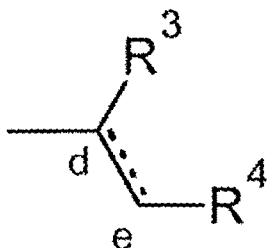
each R⁵ is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl or aralkenyl;

R⁷ is H, OH, OR⁸ wherein R⁸ is alkyl, acyl or aryl; and

R¹¹ is C₂-C₄ optionally substituted C₂-C₄ alkyl, optionally substituted aralkyl, optionally substituted cycloalkyl;

R¹² is optionally substituted aryl or R¹² is C₂-C₄ alkyl;

wherein when A is

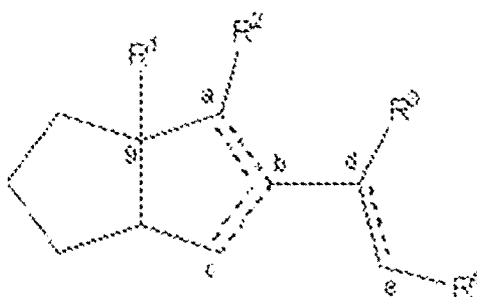


there is independently a maximum of one double bond between each of the carbon atoms of the centers a-b and b-c and d-e;

and when A is methyl, aryl or cycloalkyl there is independently a maximum of one double bond between each of the carbon atoms of the centers a-b and b-c;

for use in a method of increasing the secretion of anti-inflammatory cytokine IL-10 and/or IL4 in the leukocytes of a subject in need thereof suffering from cancer or an inflammatory disease or condition.

2. The LRH-1 agonist for use according to claim 1, wherein said agonist is a 9-substituted bicyclic [3.3.0] octane derivative having formula II



Formula II

wherein

R^1 is $-N(R^5)_2$;

R^2 is H, alkyl, halogen, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene or N-heterocyclyl which can be optionally substituted

R^3 and R^4 are independently alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, alkylene, alkenylene, cycloalkyl, cycloalkylene, halogen or N-heterocyclyl;

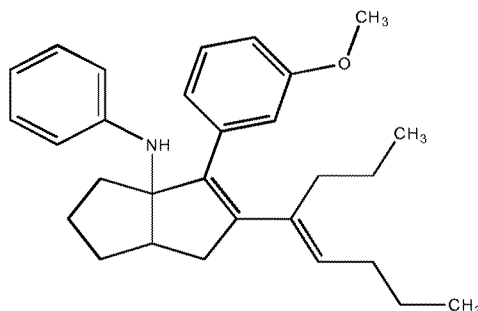
each R^5 is independently hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl or aralkenyl;

each R^6 is a straight or branched alkylene chain optionally substituted by hydroxy, mercapto, alkylthio, aryl, cycloalkyl, $-N(R^5)_2$, $-C(=O)OR^5$ or $-C(=O)N(R^5)_2$;

and wherein there is independently a maximum of one double bond between each of the carbon

atoms of the centers a-b and b-c and d-e.

3. The LRH-1 agonist for use according to claim 1 or 2, wherein said agonist is a 9-substituted bicycle [3.3.0] octane derivative having formula III



Formula III

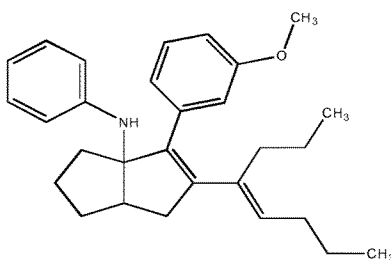
or a pharmaceutically acceptable salt thereof.

4. The LRH-1 agonist for use according to any of the precedent claims, wherein the subject in need thereof suffers from a disease selected from the list consisting of: Acute Disseminated Encephalomyelitis (ADEM); Acute necrotizing hemorrhagic leukoencephalitis; Addison's disease; Agammaglobulinemia; Alopecia areata; Amyloidosis; Ankylosing spondylitis; Anti-GBM/Anti-TBM nephritis; Antiphospholipid syndrome (APS); Autoimmune angioedema; Autoimmune aplastic anemia; Autoimmune dysautonomia; Autoimmune hepatitis; Autoimmune hyperlipidemia; Autoimmune immunodeficiency; Autoimmune inner ear disease (AIED); Autoimmune myocarditis; Autoimmune oophoritis; Autoimmune pancreatitis; Autoimmune retinopathy; Autoimmune thrombocytopenic purpura (ATP); Autoimmune thyroid disease; Autoimmune urticarial; Axonal & neuronal neuropathies; Balo disease; Behcet's disease; Bullous pemphigoid; Cardiomyopathy; Castleman disease; Celiac disease; Chagas disease; Chronic fatigue syndrome; Chronic inflammatory demyelinating polyneuropathy (CIDP) ; Chronic recurrent multifocal osteomyelitis (CRMO); Churg-Strauss syndrome; Cicatricial pemphigoid/benign mucosal pemphigoid; Crohn's disease; Cogans syndrome; Cold agglutinin disease; Congenital heart block; Coxsackie myocarditis; CREST disease; Essential mixed cryoglobulinemia; Demyelinating neuropathies; Dermatitis herpetiformis; Dermatomyositis; Devic's disease (neuromyelitis optica) ; Discoid lupus; Dressler's syndrome; Endometriosis; Eosinophilic esophagitis; Eosinophilic fasciitis; Erythema nodosum; Experimental allergic encephalomyelitis; Evans syndrome; Fibromyalgia; Fibrosing alveolitis; Giant cell arteritis (temporal arteritis); Giant cell myocarditis; Glomerulonephritis; Goodpasture's syndrome; Granulomatosis with Polyangiitis (GPA) (formerly called Wegener's Granulomatosis); Graves' disease; Guillain-Barre

syndrome; Hashimoto's encephalitis; Hashimoto's thyroiditis; Hemolytic anemia; Henoch-Schonlein purpura; Herpes gestationis; Hypogammaglobulinemia; Idiopathic thrombocytopenic purpura (ITP); IgA nephropathy; IgG4-related sclerosing disease; Immunoregulatory lipoproteins; Inclusion body myositis; Interstitial cystitis; Juvenile arthritis; Juvenile myositis; Kawasaki syndrome; Lambert-Eaton syndrome; Leukocytoclastic vasculitis; Lichen planus; Lichen sclerosus; Ligneous conjunctivitis; Linear IgA disease (LAD); Lupus (SLE); Lyme disease, chronic; Meniere's disease; Microscopic polyangiitis; Mixed connective tissue disease (MCTD); Mooren's ulcer; Mucha-Habermann disease; Multiple sclerosis; Myasthenia gravis; Myositis; Narcolepsy; Neuromyelitis optica (Devic's); Neutropenia; Ocular cicatricial pemphigoid; Optic neuritis; Palindromic rheumatism; PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus); Paraneoplastic cerebellar degeneration; Paroxysmal nocturnal hemoglobinuria (PNH); Parry Romberg syndrome; Parsonnage-Turner syndrome; Pars planitis (peripheral uveitis); Pemphigus; Peripheral neuropathy; Perivenous encephalomyelitis; Pernicious anemia; POEMS syndrome; Polyarteritis nodosa; Type I, II, & III autoimmune polyglandular syndromes; Polymyalgia rheumatica; Polymyositis; Postmyocardial infarction syndrome; Postpericardiotomy syndrome; Progesterone dermatitis; Primary biliary cirrhosis; Primary sclerosing cholangitis; Psoriasis; Psoriatic arthritis; Idiopathic pulmonary fibrosis; Pyoderma gangrenosum; Pure red cell aplasia; Raynaud's phenomenon; Reactive Arthritis; Reflex sympathetic dystrophy; Reiter's syndrome; Relapsing polychondritis; Restless legs syndrome; Retroperitoneal fibrosis; Rheumatic fever; Rheumatoid arthritis; Sarcoidosis; Schmidt syndrome; Scleritis; Scleroderma; Sjogren's syndrome; Sperm & testicular autoimmunity; Stiff person syndrome; Subacute bacterial endocarditis (SBE); Susac's syndrome; Sympathetic ophthalmia; Takayasu's arteritis; Temporal arteritis/Giant cell arteritis; Thrombocytopenic purpura (TTP); Tolosa-Hunt syndrome; Transverse myelitis; Ulcerative colitis; Undifferentiated connective tissue disease (UCTD); Uveitis; Vasculitis; Vesiculobullous dermatosis; Vitiligo; Wegener's granulomatosis (now termed Granulomatosis with Polyangiitis (GPA)).

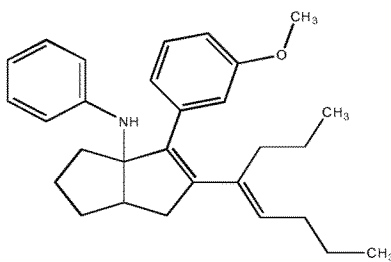
5. The LRH-1 agonist for use according to any of claims 1 to 3, wherein the subject in need thereof suffers from a disease selected from the list consisting of type I diabetes, in particular early stage type I diabetes, type II diabetes and autoimmune hepatitis.
6. The LRH-1 agonist for use according to the precedent claim, wherein the disease is early stage type I diabetes, wherein said agonist is use for the therapeutic treatment after the clinical manifestation of the disease and not for the prophylactic treatment of said disease and wherein early stage type I diabetes is defined as the stages of the diseases wherein one or all of the following criteria can be detected:

- a. Detection of islet cell autoantibodies and/or antibodies to insulin, GAD65, and tyrosine phosphatases IA-2 and IA-2beta;
 - b. Detection of ketoacidosis; and
 - c. Detection of hyperglycemia.
7. The LRH-1 agonist for use according to claim 5, wherein the disease is type II diabetes and wherein said agonist is use for the therapeutic treatment after the clinical manifestation of the disease and not for the prophylactic treatment of type II diabetes.
8. The LRH-1 agonist for use according to claim 1 or 2, wherein said agonist is a 9-substituted bicycle [3.3.0] octane derivative having formula III



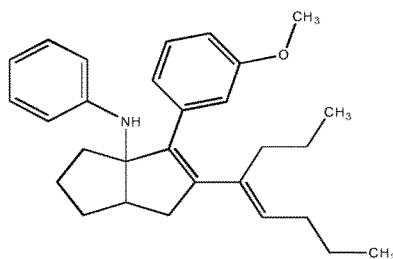
or a pharmaceutically acceptable salt thereof and wherein the subject in need thereof suffers from a disease selected from the list consisting of type I diabetes, in particular early stage type I diabetes, type II diabetes and autoimmune hepatitis.

9. The LRH-1 agonist for use according to claim 1 or 2, wherein said agonist is a 9-substituted bicycle [3.3.0] octane derivative having formula III



or a pharmaceutically acceptable salt thereof and wherein the subject in need thereof suffers from early stage type I diabetes as defined in claim 6 above and wherein said agonist is use for the therapeutic treatment and not for the prophylactic treatment of said disease.

10. The LRH-1 agonist for use according to claim 1 or 2, wherein said agonist is a 9-substituted bicycle [3.3.0] octane derivative having formula III



or a pharmaceutically acceptable salt thereof and wherein the subject in need thereof suffers from type II diabetes and wherein said agonist is use for the therapeutic treatment and not for the prophylactic treatment of said disease.

11. The LRH-1 agonist as defined in any of the precedent claims for use in a method of improving glucose tolerance in a subject in need thereof suffering from type II diabetes.
12. The LRH-1 agonist as defined in any of the precedent claims for use according to claim 1, wherein the subject in need thereof suffers from cancer.
13. The LRH-1 agonist for use according to any of the preceding claims, wherein the agonist is administered via oral, intraarterial or intravenous.
14. A method for enhancing the endogenous production of interleukin-10 (IL-10) in mammalian cells or tissues, comprising administering to a subject in need thereof an effective amount of a compound according to any of claims 1 to 3 or a pharmaceutically acceptable salt thereof.
15. A method for treating type I diabetes, in particular early stage type I diabetes, type II diabetes or autoimmune hepatitis, comprising administering to a subject in need thereof an effective amount of a compound according to any of claims 1 to 3 or a pharmaceutically acceptable salt thereof.
16. A method for improving glucose tolerance in a subject suffering from type II diabetes comprising administering to said subject in need thereof an effective amount of a compound according to any of claims 1 to 3 or a pharmaceutically acceptable salt thereof.

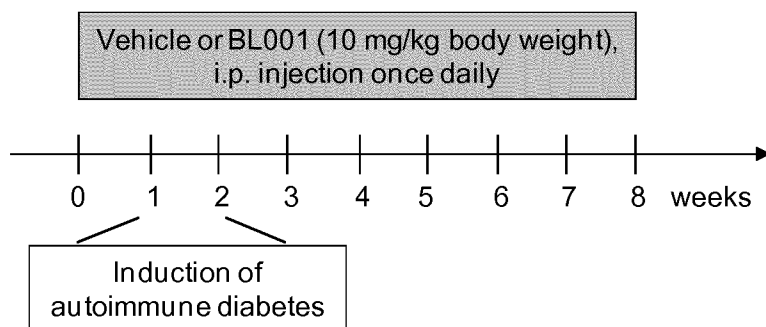
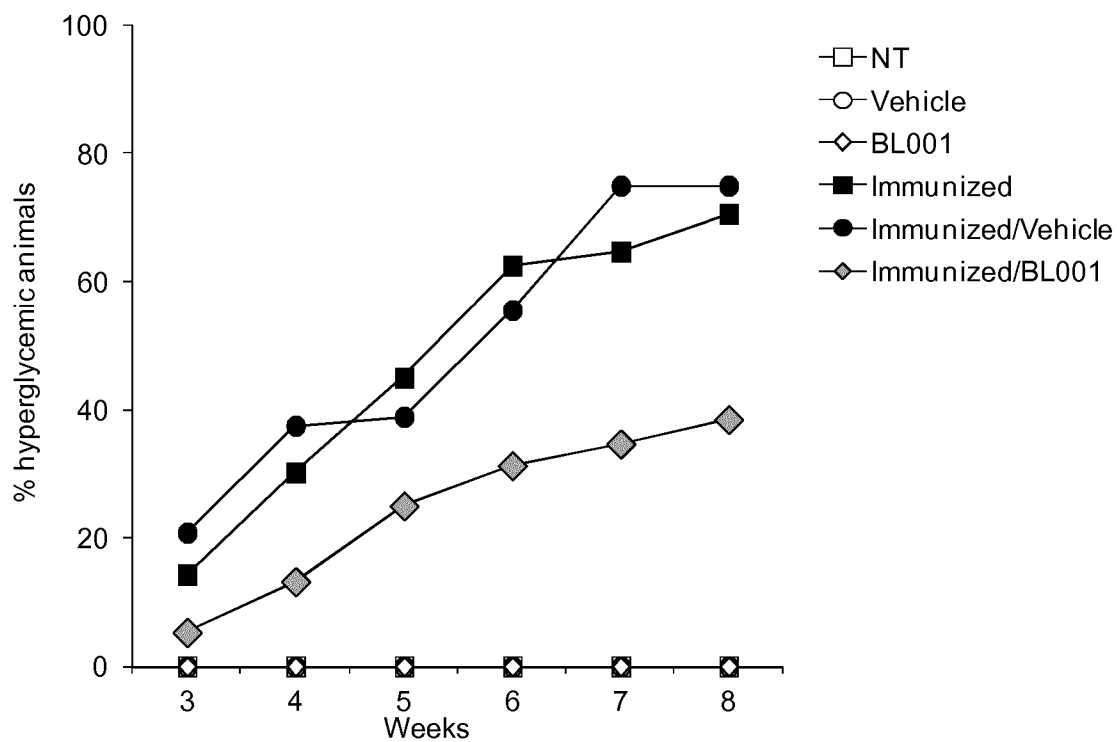
A**B**

Fig. 1

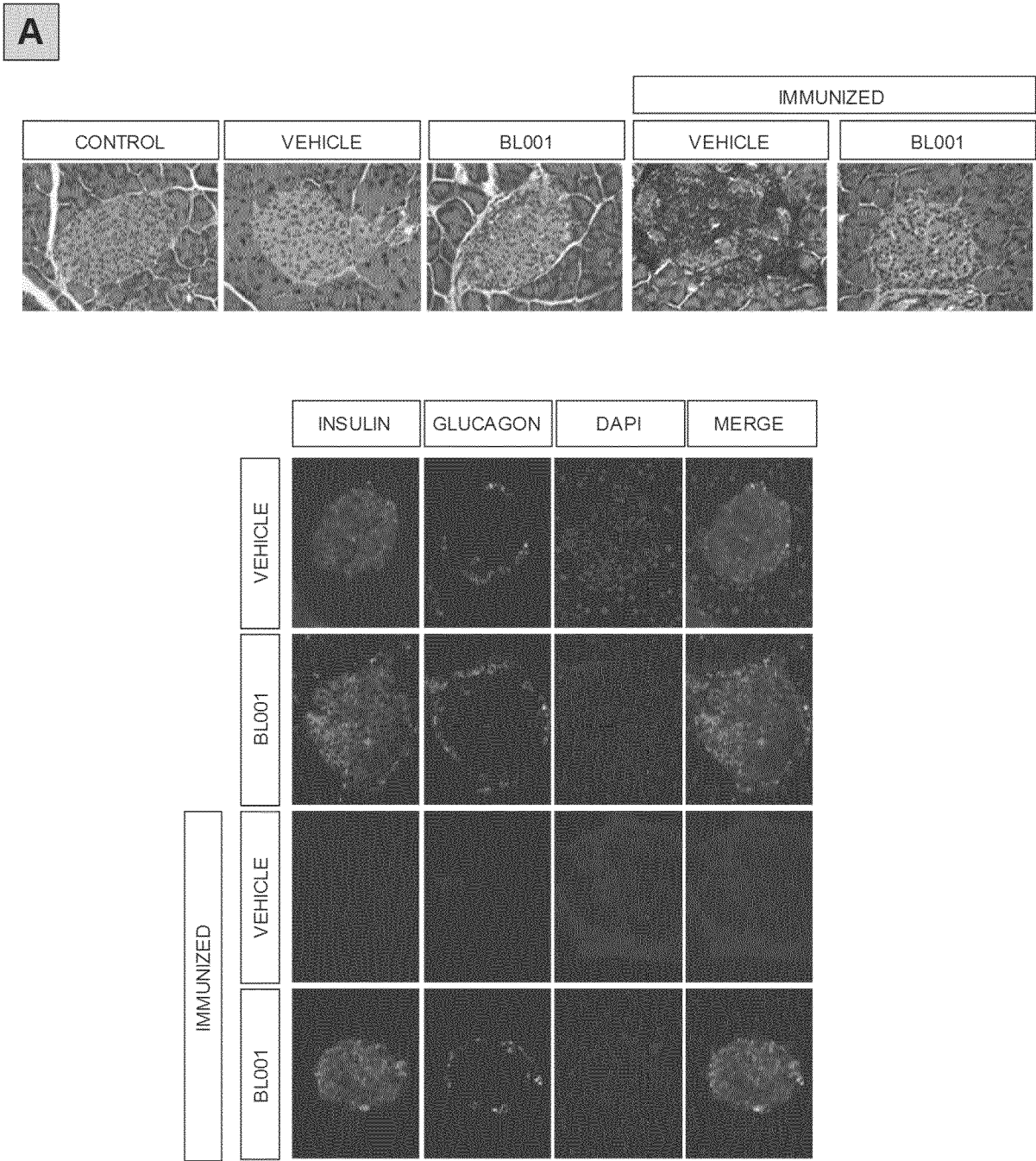


Fig. 2

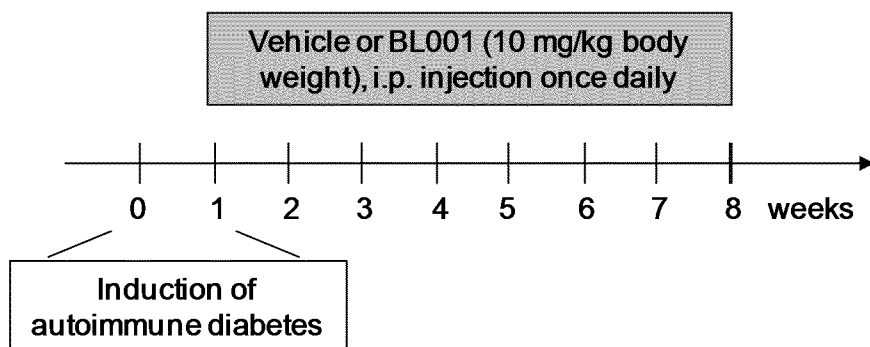
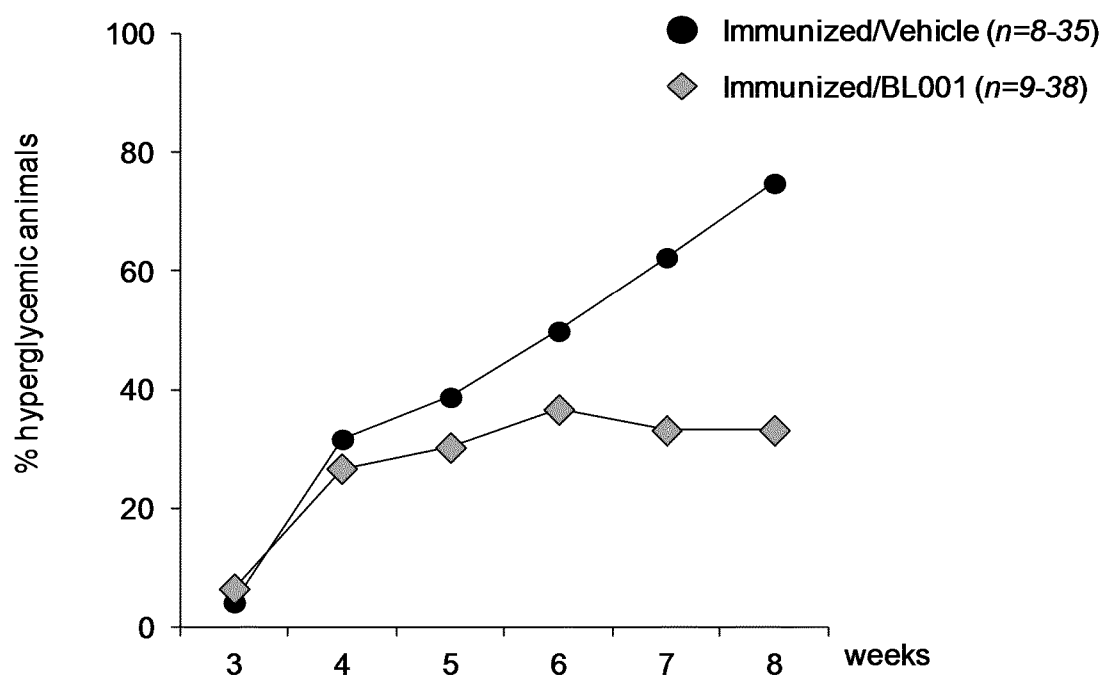
A**B**

Fig. 3

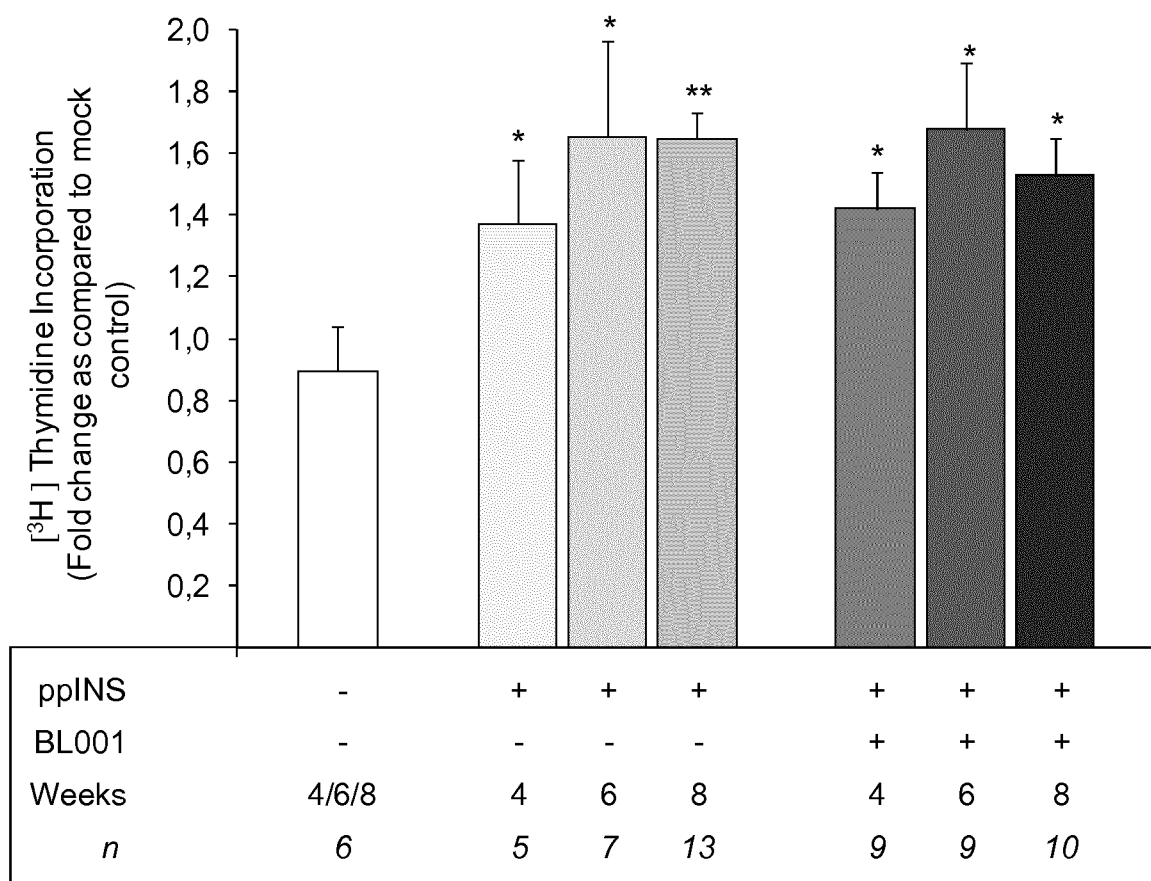


Fig. 4

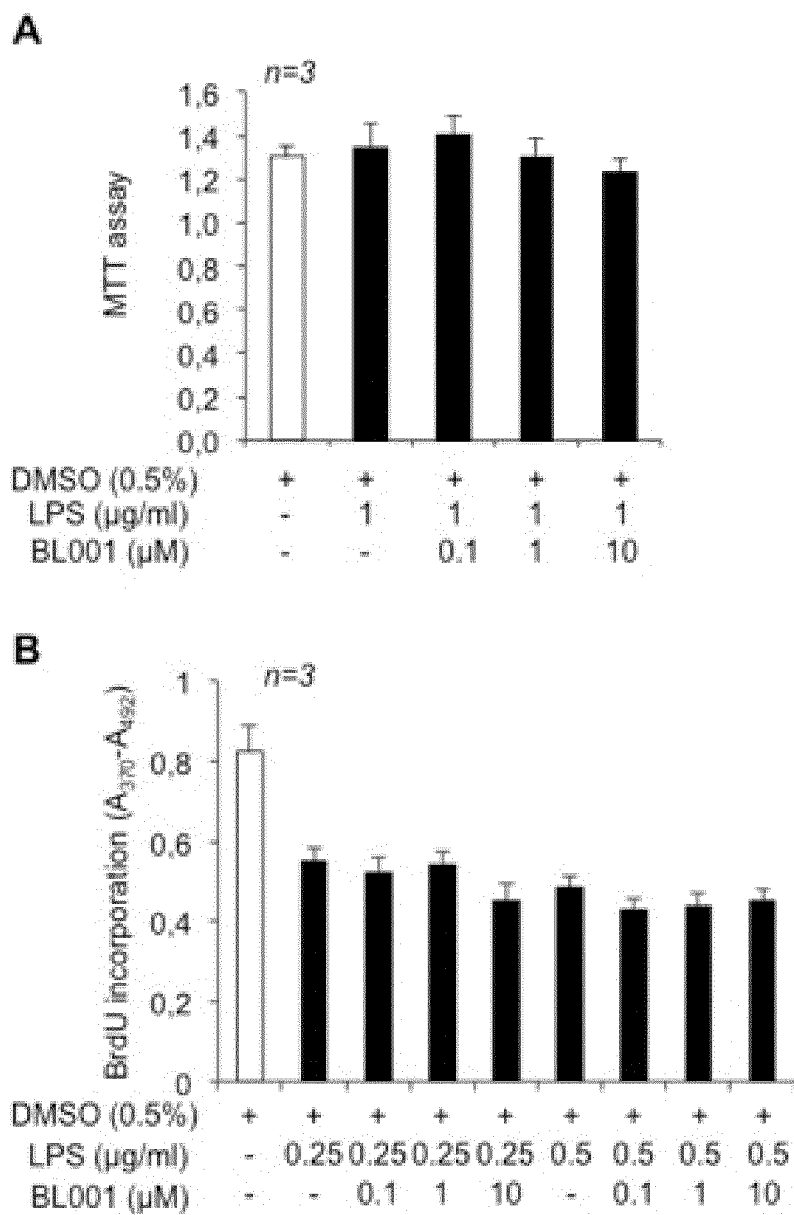


Fig. 5

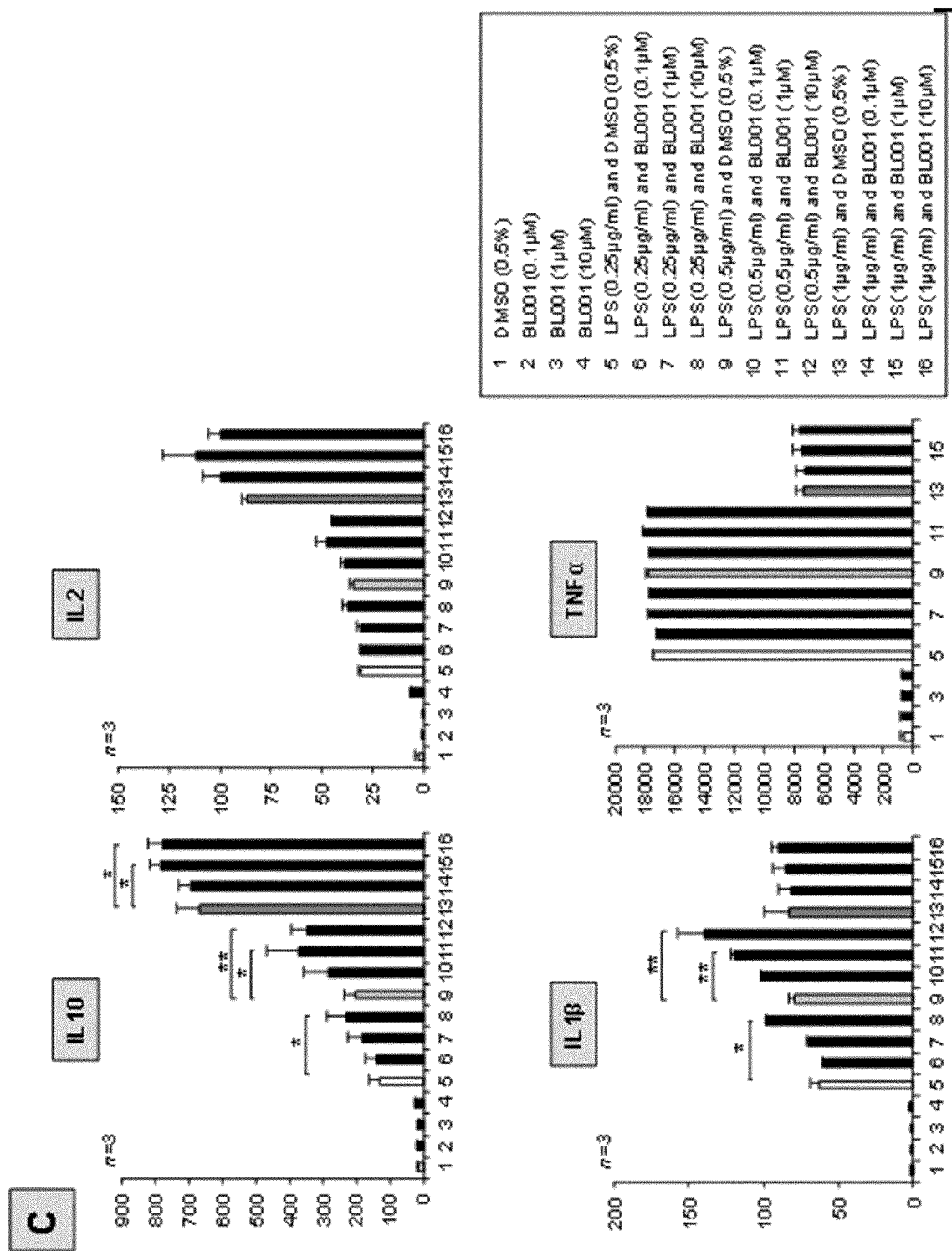


Fig. 5 (cont.)

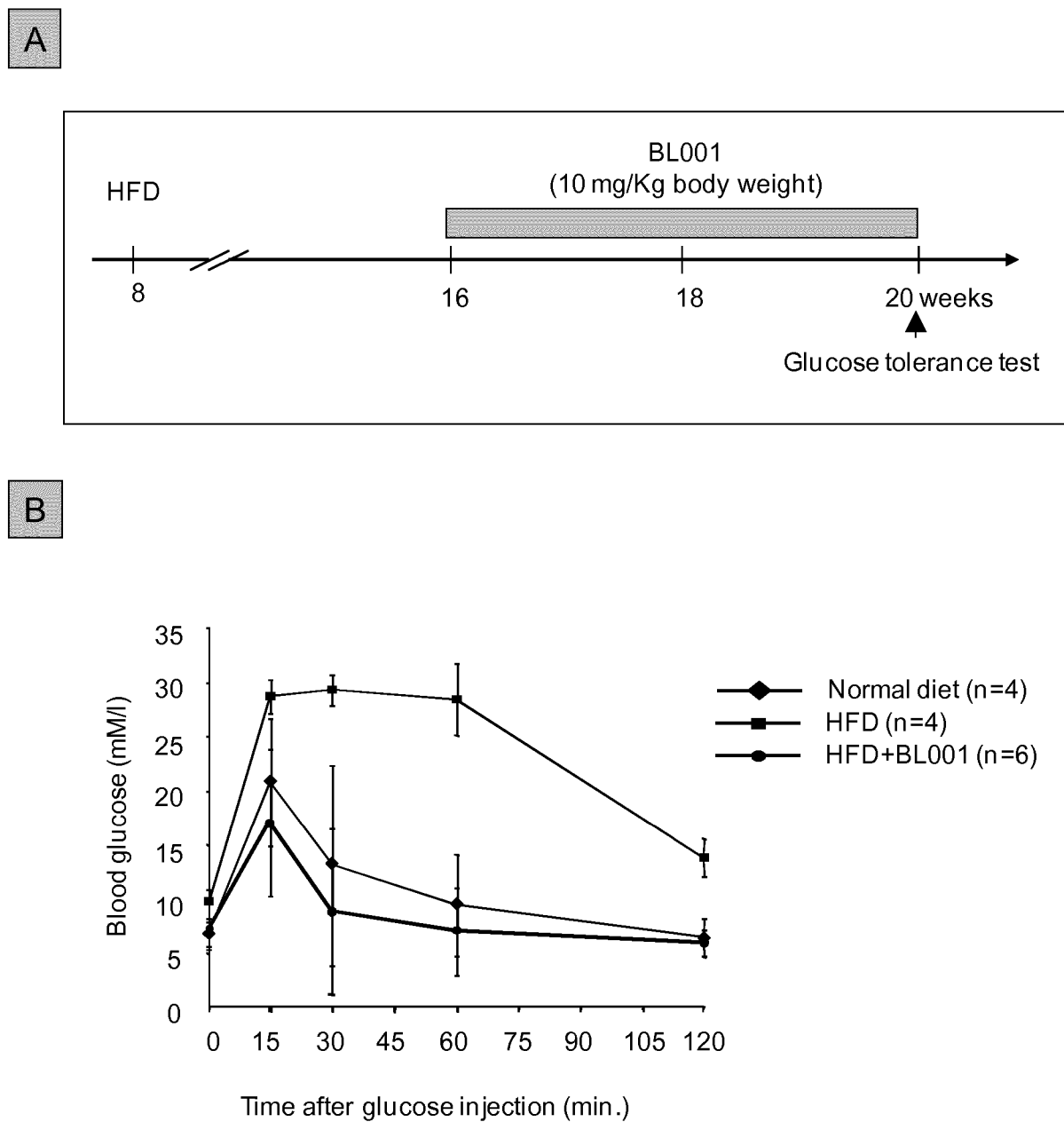


Fig. 6

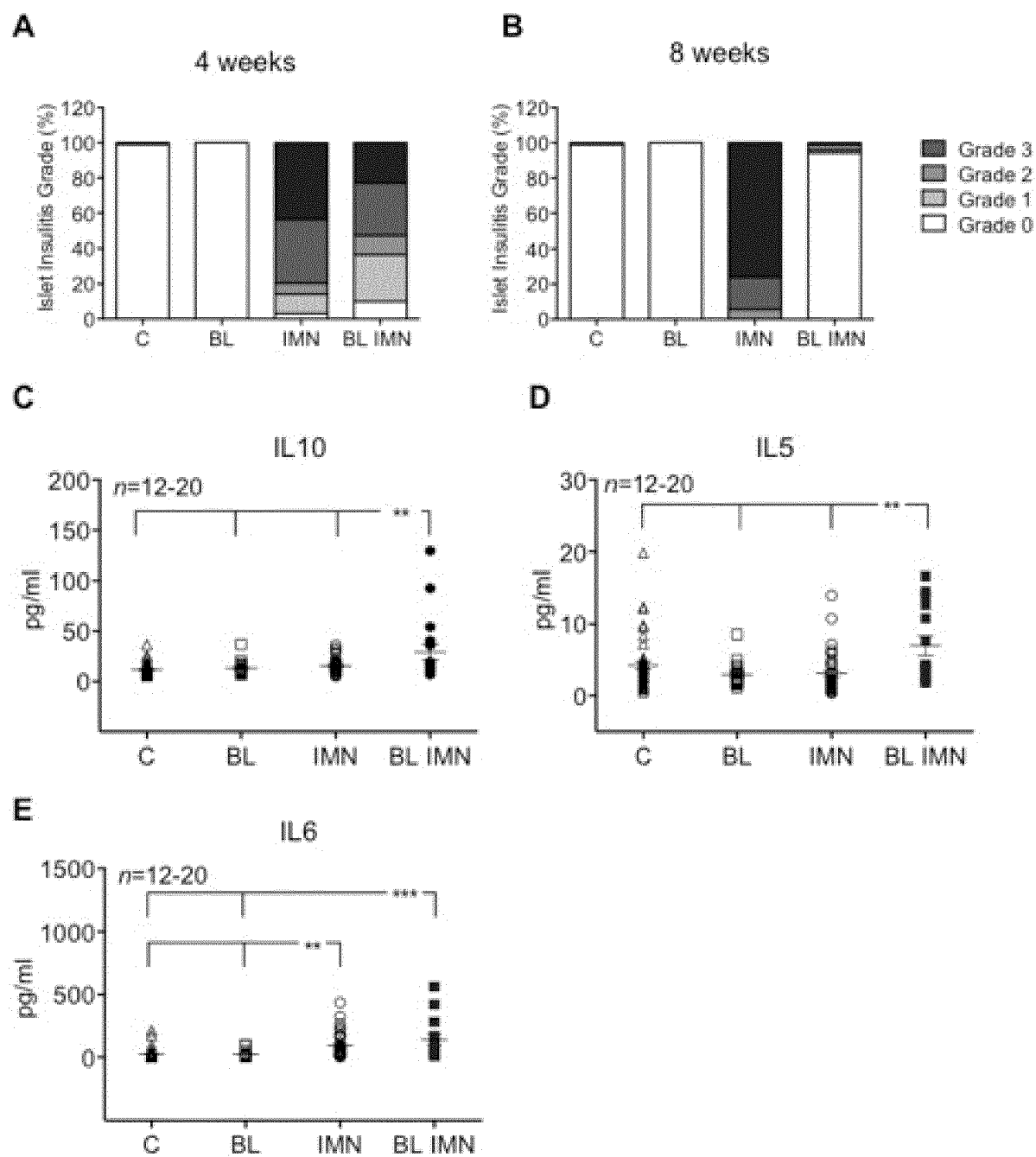


Fig. 7

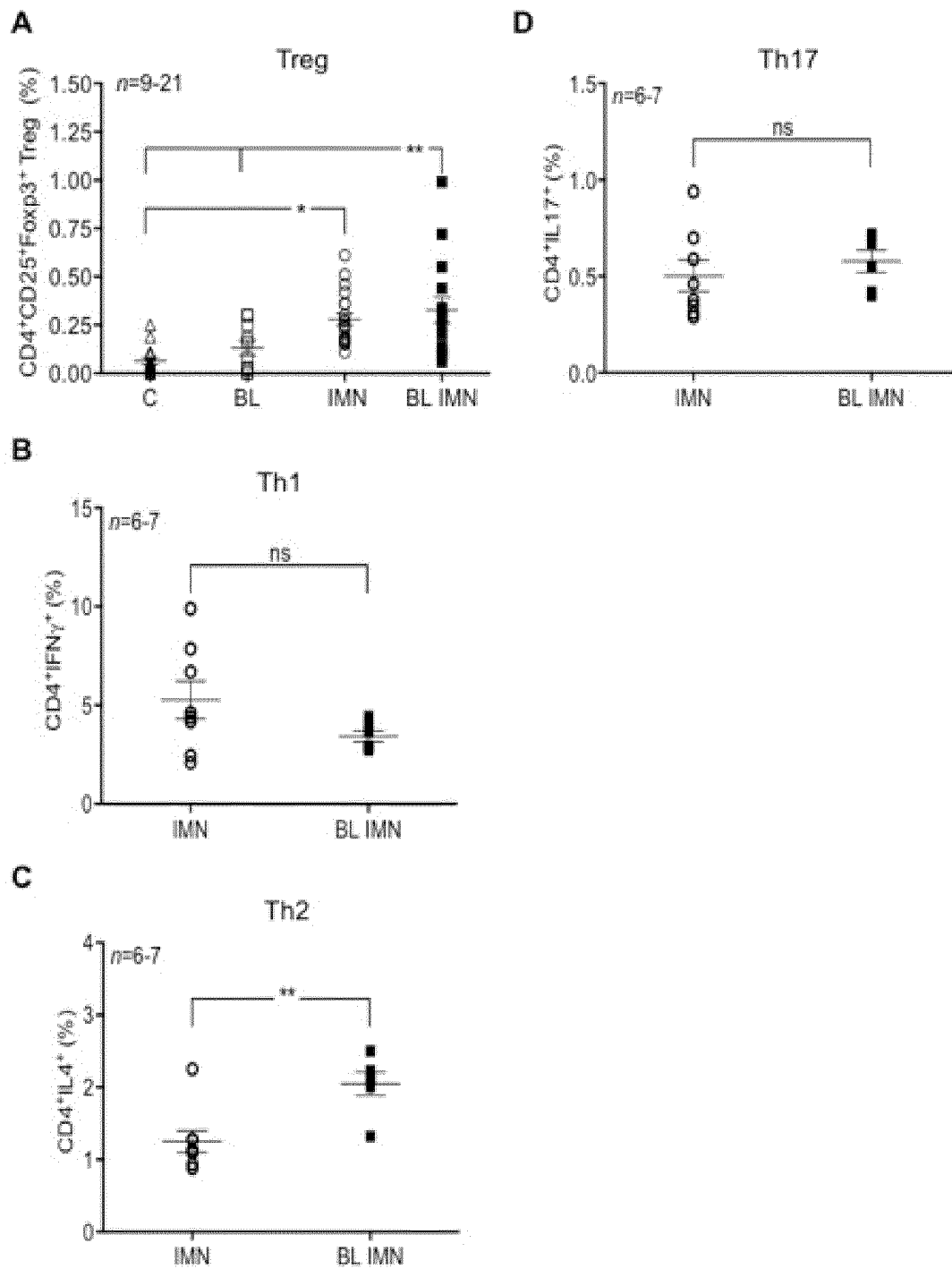


Fig. 8

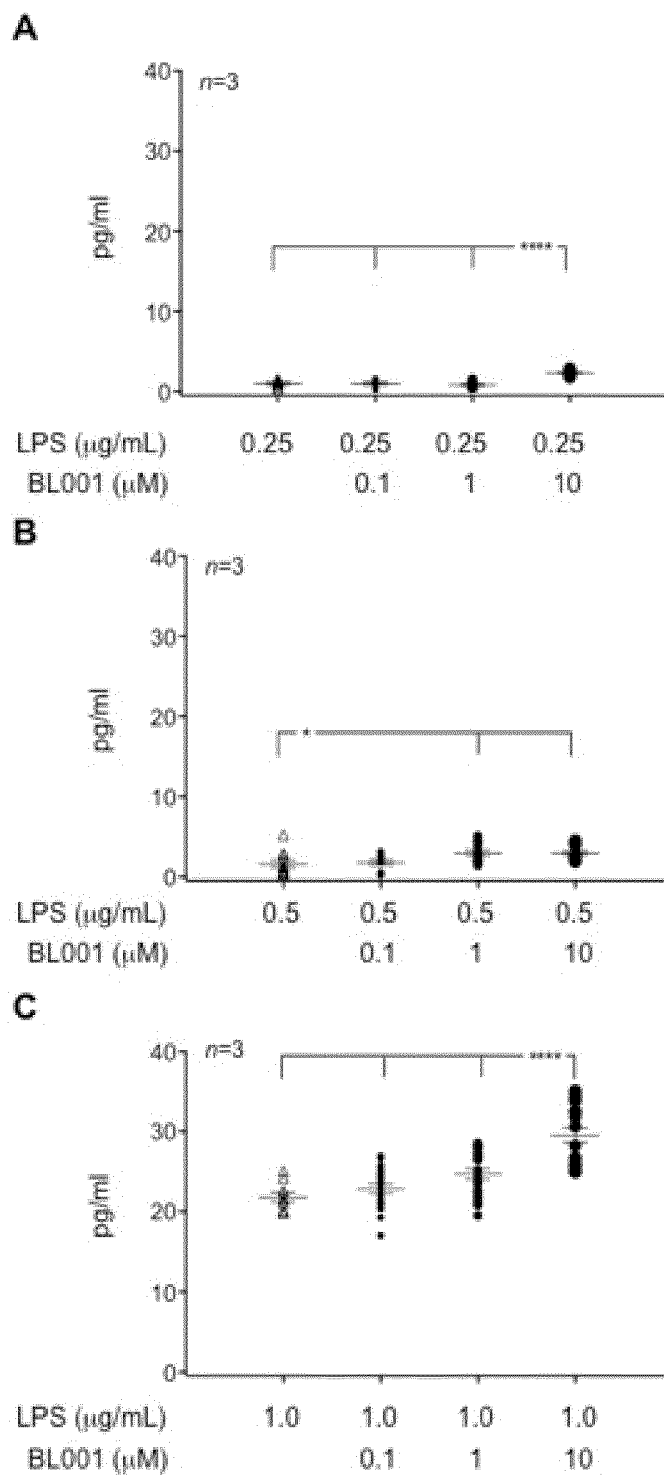


Fig. 9

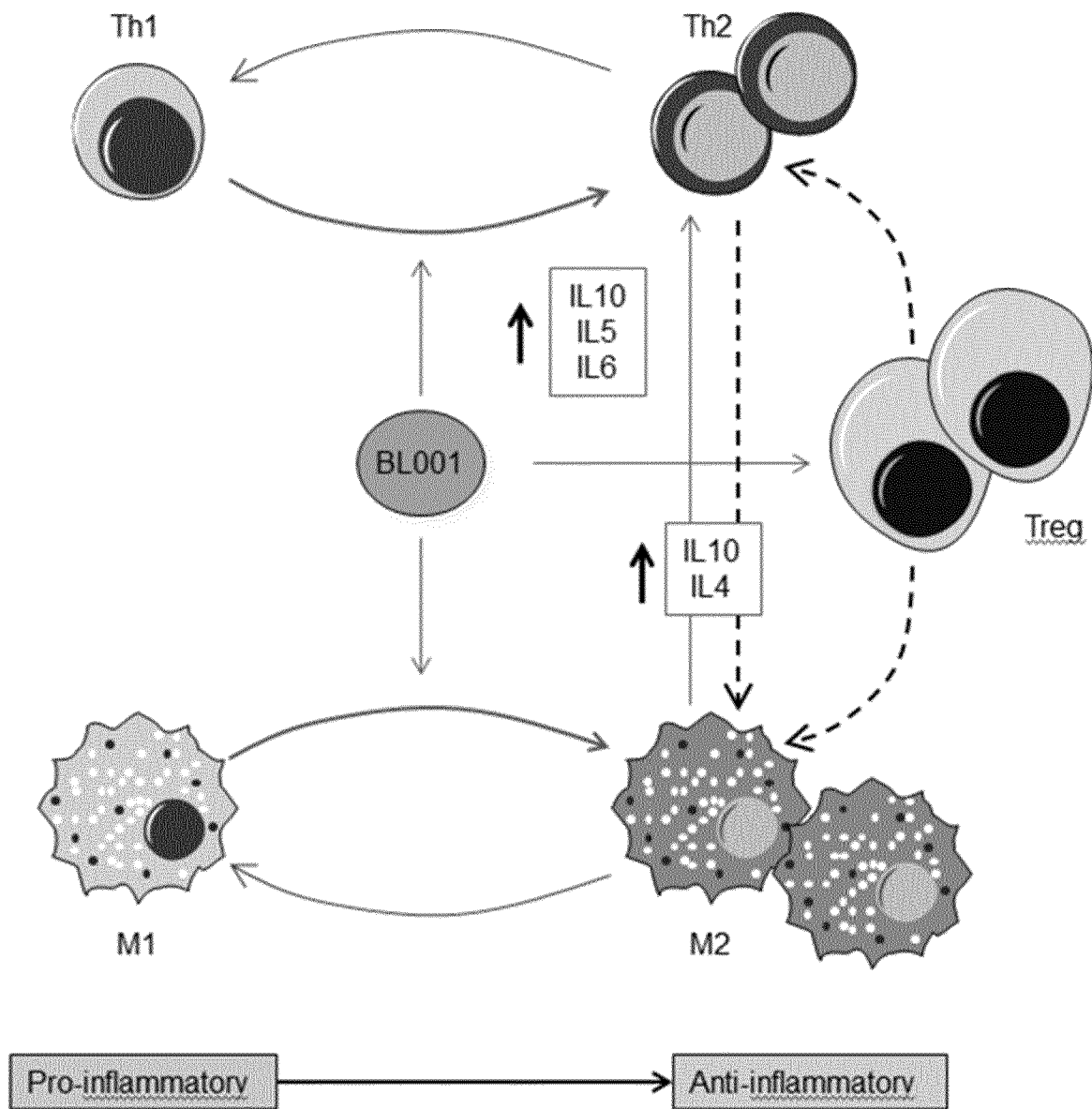


Fig. 10

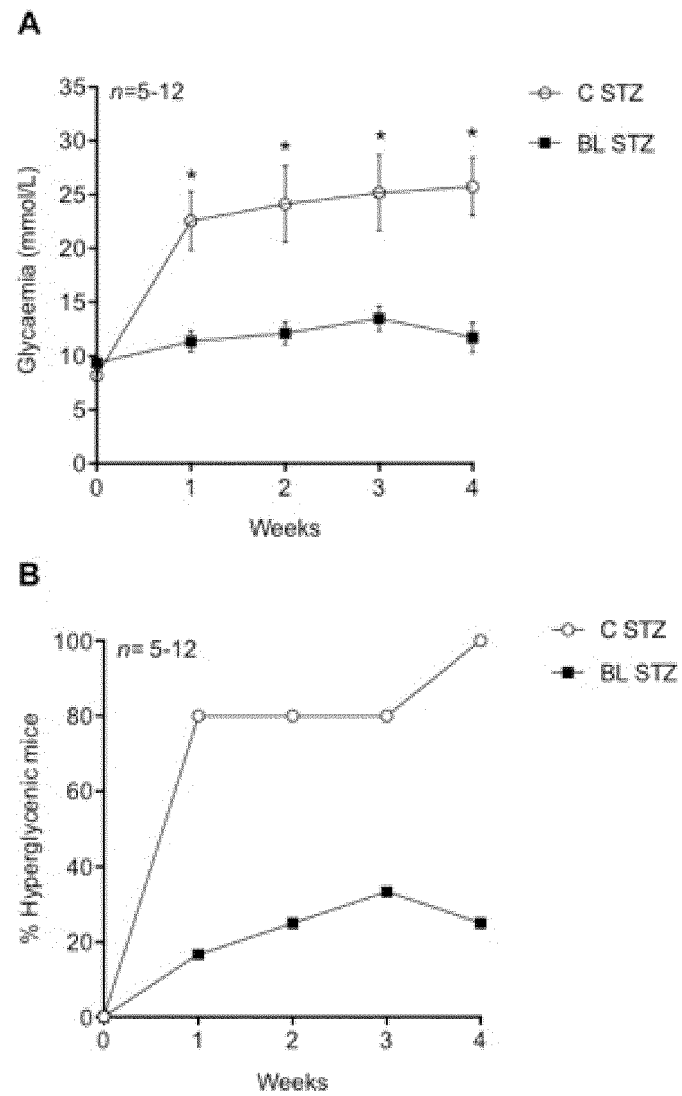


Fig. 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/057137

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/136 A61P3/10 A61P37/06 A61P1/16 A61P35/00 A61P29/00 ADD. 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) A61K 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) EPO-Internal, CHEM ABS Data, BIOSIS, WPI Data								
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td> WO 2011/144725 A2 (FUNDACION PUBLICA ANDALUZA PROGRESO Y SALUD [ES]; ST-ONGE LUC [DE]; GA) 24 November 2011 (2011-11-24) cited in the application page 1, paragraph 1 page 5, paragraph 25 - page 6, paragraph 27 page 7, paragraph 33 - page 8, paragraph 33 page 34, paragraph 118 - page 35, paragraph 119 page 36, paragraph 122 page 42, paragraph 146 - page 44, paragraph 154; claims; examples ----- -/-- </td> <td>1-16</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	WO 2011/144725 A2 (FUNDACION PUBLICA ANDALUZA PROGRESO Y SALUD [ES]; ST-ONGE LUC [DE]; GA) 24 November 2011 (2011-11-24) cited in the application page 1, paragraph 1 page 5, paragraph 25 - page 6, paragraph 27 page 7, paragraph 33 - page 8, paragraph 33 page 34, paragraph 118 - page 35, paragraph 119 page 36, paragraph 122 page 42, paragraph 146 - page 44, paragraph 154; claims; examples ----- -/--	1-16
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.						
X	WO 2011/144725 A2 (FUNDACION PUBLICA ANDALUZA PROGRESO Y SALUD [ES]; ST-ONGE LUC [DE]; GA) 24 November 2011 (2011-11-24) cited in the application page 1, paragraph 1 page 5, paragraph 25 - page 6, paragraph 27 page 7, paragraph 33 - page 8, paragraph 33 page 34, paragraph 118 - page 35, paragraph 119 page 36, paragraph 122 page 42, paragraph 146 - page 44, paragraph 154; claims; examples ----- -/--	1-16						
☒ 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 11 May 2016		Date of mailing of the international search report 27/05/2016						
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Hoff, Philippe						

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/057137

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	COBO-VUILLEUMIER N ET AL: "The LRH-1 agonist BL001 improves human islet survival and blunts development of hyperglycaemia in the RIP-B7.1 mouse model of experimental autoimmune diabetes", DIABETOLOGIA, vol. 56, no. Suppl. 1, ABST 166, September 2013 (2013-09), XP002757571, & 49TH ANNUAL MEETING OF THE EUROPEAN-ASSOCIATION-FOR-THE-STUDY-OF-DIABETES (EASD); BARCELONA, SPAIN; SEPTEMBER 23 -27, 2013 ISSN: 0012-186X the whole document -----	1-11, 13-16
X	Baquet Mathurin: "Role of LRH-1/NR5A2 in islet physiology and pathophysiology", Doctoral Thesis, 2010, pages 129-133, XP002757572, Retrieved from the Internet: URL: https://archive-ouverte.unige.ch/unige:12586 [retrieved on 2016-05-11] page 11: Summary pages 129-133: Chapter V- Discussions and perspectives -----	1-11, 13-16
A	RICHARD J. WHITBY ET AL: "Identification of Small Molecule Agonists of the Orphan Nuclear Receptors Liver Receptor Homolog-1 and Steroidogenic Factor-1", JOURNAL OF MEDICINAL CHEMISTRY, vol. 49, no. 23, 1 November 2006 (2006-11-01), pages 6652-6655, XP055005441, ISSN: 0022-2623, DOI: 10.1021/jm060990k the whole document ----- -/--	1-16

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LALIT MANISHA ET AL: "A combined pharmacophore modeling, 3D-QSAR and molecular docking study of substituted bicyclo-[3.3.0]oct-2-enes as liver receptor homolog-1 (LRH-1) agonists", JOURNAL OF MOLECULAR STRUCTURE, vol. 1049, 2013, pages 315-325, XP028705415, ISSN: 0022-2860, DOI: 10.1016/J.MOLSTRUC.2013.06.035 the whole document	1-16
A	WO 2005/082344 A1 (SMITHKLINE BEECHAM CORP [US]; GOODWIN BRYAN JAMES [US]; STEWART EUGENE) 9 September 2005 (2005-09-09) abstract; claims; examples	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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