(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 February 2001 (01.02.2001)

PCT

(10) International Publication Number
WO 01/07054 A1

(51) International Patent Classification[7]: A61K 31/7076, 31/7056, 45/06, A61P 37/00, 37/06, A61K 31/00

(21) International Application Number: PCT/US00/20081

(22) International Filing Date: 21 July 2000 (21.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/145,365	22 July 1999 (22.07.1999)	US
09/620,254	20 July 2000 (20.07.2000)	US

(71) Applicant *(for all designated States except US)*: SUPERGEN, INC. [US/US]; Suite 220, Two Annabel Lane, San Ramon, CA 94583 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ENNS, Timothy [US/US]; 7367 Elmwood Circle, Pleasanton, CA 94588 (US). DANG, Nam, H. [US/US]; 4101 Marlowe Street, Houston, TX 77005 (US).

(74) Agent: WEITZ, David, J.; Wilson Sonsini Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94304-1050 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/07054 A1

(54) Title: METHODS FOR TREATING AUTOIMMUNE DISEASES

(57) Abstract: The present invention provides methods for treating a patient with an autoimmune disease by administering an anti-ADA agent such as an ADA inhibitor, such as pentostatin.

METHODS FOR TREATING AUTOIMMUNE DISEASES

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to treatment of autoimmune diseases and more specifically to the administration of inhibitors of adenosine such as pentostatin and analogs and derivatives thereof.

Description of Related Art

A wide range of degenerative diseases, the so-called autoimmune diseases, are caused by the immune system attacking a person's own cells. Autoimmune diseases are characterized by such immuno-dysfunction that circulating autoantibodies or cells are generated directing against normal autologous tissues.

Initiation of autoimmune diseases is not well understood, but involves both genetic predisposition and environmental factors. Such diseases are usually classified clinically in a variety of ways. In light of affected parts by the diseases, there are, for example, degenerative diseases of supporting tissues and connective tissues; autoimmune degenerative diseases of salivary glands, particularly Sjogren's disease; autoimmune degenerative diseases of kidneys, particularly systemic lupus erythematodes (SLE) and glomerulonephritis; autoimmune degenerative diseases of joints, particularly rheumatoid arthritis; and autoimmune degenerative diseases of blood vessels such as generalized necrotizing angitis and granulomatous angitis; and multiple sclerosis. Alternatively, autoimmune diseases can be classified in one of the two different categories: cell-mediated disease (i.e. T-cell) or antibody mediated disorders. Examples of cell-mediated autoimmune

diseases include multiple sclerosis, rheumatoid arthritis, autoimmune thyroiditis, and diabetes mellitus. Antibody-mediated autoimmune disorders include myasthenia gravis and SLE.

The current treatments for both categories of autoimmune diseases involve administration of drugs such as methotrexate, cyclophosphamide, azathioprine and cyclosporin A. Steroid compounds such as prednisone and methylprednisilone are also employed in regimen.

Other strategies have been developed to target autoantibody. For example, antigen-based heteropolymers have been used to specifically target both complementary receptor site (CR1) on a primate erythrocyte and a target pathogenic autoantibody (U.S Patent No. 5,879,679). In the heteropolymer, a monoclonal antibody specific for binding to a CR1 site on a primate erythrocyte is cross linked to an antigen specific for a target pathogenic autoantibody.

There still exists the need for improved treatment for autoimmune diseases which acts on the immune system and which has a function mechanism different from those currently available.

SUMMARY OF THE INVENTION

The present invention provides novel methods for treating autoimmune diseases by exploiting the signal transduction pathways of T-cell activation via ADA and CD26. Applicants believe that by inhibiting ADA- and CD26-mediated T lymphocyte activation, inflammatory responses of the body and symptoms of the autoimmune disease should be reduced.

A method is provided which comprises administrating to a patient suffering from an autoimmune disease in need thereof a therapeutically effective amount of an anti-ADA agent. The anti-ADA agent may either

act as an ADA enzyme inhibitor to prevent the enzyme from deaminating adenosine, or bind to ADA to prevent ADA from binding to the T-cell surface CD26.

According to this embodiment, the anti-ADA agent is may be an analog or derivative of adenosine which can bind to ADA but cannot be deaminated. Examples of such adenosine analogs and derivatives include, but are not limited to, pentostatin (2'-deoxycoformycin), fludarabine monophosphate, 2-chloro-2'-deoxyadenosine, 2'-deoxyadenosine, 3'-deoxyadenosine and dideoxyadenosine.

The anti-ADA agents can be administrated into a patient with an autoimmune disease in many pharmaceutically-acceptable ways. The anti-ADA agent can be administrated intravenously, intramuscularly, orally, by inhalation, parenterally, intraperitoneally, intraarterially, transdermally, sublingually, nasally, through use of suppositories, transbuccally, liposomally, adiposally, intraocularly, subcutaneously, intraarticularly, intrathecally, topically, or through local administration.

In one variation of the embodiment, the method comprises administrating pentostatin to the patient.

According to this variation, pentostatin is administrated orally by incorporating into an orally dosage form such as tablets and soft or hard gel capsules. For example, pentostatin may be administrated orally in the form of a tablet.

In another variation of the embodiment, pentostatin is administrated parenterally by dissolving in a pharmaceutically-acceptable solvent such as saline or other infusion fluids. For example, pentostatin may be dissolved in a solution comprising pentostatin.

The solution above may further include an excipient in an amount sufficient to enhance the stability of the solution. Examples of the excipient includes, but are not limited to, sorbitol, mannitol and

cyclodextrin such as α-, β-, and γ-cyclodextrin and modified, amorphous cyclodextrin such as hydroxy-substituted α-, β–, and γ–cyclodextrin.

The anti-ADA agents according to the present invention can be administered alone or in combination with each other. For example, pentostatin may be coadministered with deoxyadenosine to enhance inhibition of T lymphocyte. The anti-ADA agents can also be used in combination with other drugs known for the treatment of autoimmune diseases, such as cyclosporin A, methotrexate, cyclophosphamide, azathiprine and steroids. Alternatively, the anti-ADA agent can be coadministered with a H2 blocker such as cimetidine to enhance the bioavailability of the anti-ADA agent.

The method can be used to treat patients suffering from autoimmune diseases such as multiple sclerosis, Graves' disease, systemic lupus erythematosus, diabetes mellitus, aseptic meningitus, systemic scleroderma, adult-onset idiopathic hypoparathyroidism and membranous glomerulonephritis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel methods for treating autoimmune diseases. In essence, the method comprises administrating to a patient suffering from the autoimmune disease a therapeutically effective amount of an anti-ADA agent such as an adenosine analog.

It is believed that the method operates by exploiting the signal transduction pathways of T-lymphocyte or T-cell activation via ADA and CD26. It is also believed that by inhibiting ADA- and CD26-mediated T lymphocyte activation, inflammatory responses of the body and symptoms of the autoimmune disease should be reduced.

1. Autoimmune Diseases

Autoimmune diseases refer to a wide range of degenerative diseases caused by the immune system attacking a person's own cells. Autoimmune diseases are usually classified clinically in a variety of ways. In light of affected parts by the diseases, there are, for example, degenerative diseases of supporting tissues and connective tissues; autoimmune degenerative diseases of salivary glands, particularly Sjogren's disease; autoimmune degenerative diseases of kidneys, particularly systemic lupus erythematodes (SLE) and glomerulonephritis; autoimmune degenerative diseases of joints, particularly rheumatoid arthritis; and autoimmune degenerative diseases of blood vessels such as generalized necrotizing angitis and granulomatous angitis; and multiple sclerosis. Alternatively, autoimmune diseases can be classified in one of the two different categories: cell-mediated disease (i.e. T-cell) or antibody mediated disorders. Examples of cell-mediated autoimmune diseases include multiple sclerosis, rheumatoid arthritis, autoimmune thyroiditis, and diabetes mellitus. Antibody-mediated autoimmune disorders include myasthenia gravis and SLE.

2. CD26 and ADA

CD26 is a 110-kD cell surface glycoprotein and widely distributed on epithelial cells of various tissues, including the liver, kidney and intestine. CD26 is generally expressed on the CD4 memory/helper population and also strongly expressed on subsets of both activated CD4 and CD8 T-cells (Fox, D.A. et al. (1984) J. Immunol. 133:1250-1256). This unique population of human CD4 cells is the only one that can respond to recall antigens, induce B-cell immunoglobulin (IgG) synthesis and activate MHC-restricted cytotoxic T cells (Dang, N.H. et al. (1990) J. Immunol. 144:4092-4100).

CD26 is ecto-enzyme that resides on the cell surface and has dipeptidyl peptidase IV (DPPIV) activity. This ecto-enzyme can cleave Xaa-Pro or Xaa-Ala dipeptides from the N-termini of polypeptides (Watanabe, Y. et al. (1993) Res. Commun. Chem. Pathol. Pharmacol. 81:323-330).

Recently CD26 has been found to be highly expressed on the surface of T-cells from patients suffering from autoimmune diseases such as multiple sclerosis, diabetes mellitus, rheumatoid arthritis, Graves' disease and systemic lupus erythematodes (SLE) (Constantinescu, C.S,. et al. (1995) J. Neurol. Sci. 130: 178-182; Mizokami A. et al. (1996) J. Rheumatol. 23:2022-2026; Golubovic E. et al. (1996) Srp. Arh. Celok. Lek. 124: Suppl. 1:43-44; Nishkawa, Y. et al. (1995) Rinsho Byori 43:1057-1060; Plana M. et al. (1994) Clin. Immunol. Immunopathol. 72: 227-232).

ADA is a 41 kD protein expressed in all tissues with highest expression in lymphocytes. ADA participates in the purine metabolism where it degrades either adenosine or 2'-deoxyadenosine producing inosine or 2'-deoxyinosine, respectively. It has been found that the activity of ADA is subject to changes depending upon the degree of activity of the cell, i.e. whether differentiation or proliferation occurs (Trotta, P.P. and Balis M.E. (1977) Cancer Research 37: 2297-2305).

3. Methods for Treating Autoimmune Diseases

In one embodiment, a method is provided which comprises administrating to a patient suffering from an autoimmune disease a therapeutically effective amount of an anti-ADA agent. The anti-ADA agent may either act as an ADA enzyme inhibitor to prevent the enzyme from deaminating adenosine, or binds to ADA to prevent ADA from binding to the T-cell surface CD26.

According to this embodiment, the anti-ADA agent is a structural analog of adenosine which binds to ADA but cannot be deaminated. Examples of such anti-ADA agent includes, but are not limited to, pentostatin (2'-deoxycoformycin or NIPENT®), fludarabine monophosphate, 2-chloro-2'-deoxyadenosine, 2'-deoxyadenosine, 3'-deoxyadenosine and dideoxyadenosine. Prodrugs of these anti-ADA agents such as phosphates, esters and amides may also be used in the practice of this invention. For example, prodrugs of pentostatin may be used to increase bioavailability through selective bioconversion.

In particular, pentostatin is a tight-binding inhibitor of ADA which has been used as a therapeutic agent for a number of disorders including hairy cell leukemia and acute lymphocytic leukemia. 2'-deoxycoformycin is available as NIPENT® (Supergen, San Ramon, CA).

Pentostatin is believed to act in vivo to increase adenosine concentration by inhibiting adenosine deaminase through competitive binding. Such binding is biologically quite tight, with a binding coefficient of K_i of 2.5×10^{-12}M. Through this inhibition, pentostatin may slow in vivo degradation of adenosine and/or prevent ADA from binding to CD26, thus increasing the concentration and activity of adenosine near the cell surface of T cells.

Pentostatin has been used in the laboratory to mimic the effects of inherited adenosine deaminase deficiency which is the underlying biochemical defect in 1/3 to 1/2 of cases of non-X-linked severe combined immunodeficiency syndrome. Mitchell, B. et al., "Purinogenic immunodeficiency disease: Clinical features and molecular mechanisms", *Ann Int. Med.* **92**:826-831m (1980). The clinical use of pentostatin has primarily been with T lymphocyte malignancies including T-cell acute lymphocytic leukemia, lymphocytic lymphoma, chronic lymphocytic leukemia and mycosis fungoides (Sezary Syndrome).

The anti-ADA agent can be incorporated into a variety of formulations for the treatment of autoimmune diseases. More particularly, the anti-ADA agent can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and may be formulated into preparation in solid, semi-solid, or liquid forms, such as tablets, capsules, pills, powders, granules, dragees, gels, slurries, ointments, solutions, suppositories, injections, inhalants and aerosols.

The anti-ADA agent can be administrated into a patient with an autoimmune disease in many pharmaceutically-acceptable ways. The anti-ADA agent can be administrated intravenously, intramuscularly, orally, by inhalation, parenterally, intraperitoneally, intraarterially, transdermally, sublingually, nasally, through use of suppositories, transbuccally, liposomally, adiposally, intraocularly, subcutaneously, intraarticularly, intrathecally, topically, or through local administration.

The anti-ADA agents can be administered alone, in combination with each other, or they can be used in combination with other drugs known for the treatment of autoimmune diseases, such as cyclosporin A, methotrexate, cyclophosphamide, azathioprine and steroids (e.g. prednisone and methyprednisone).

For injection, the anti-ADA agents can be formulated into preparations by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives. Preferably, the anti-ADA agents may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the

barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the anti-ADA agents can be formulated readily by combining with pharmaceutically acceptable carriers that are well known in the art. Such carriers enable the compounds to be formulated as tablets, pills, dragees, capsules, emulsions, lipophilic and hydrophilic suspensions. liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient with an autoimmune disease. Pharmaceutical preparations for oral use can be obtained by mixing the anti-ADA agent with a solid excipient, optionally grindign a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylprrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium

In the oral dosage forms, it may be useful to include antioxidants or preservatives. Antioxidants that may be used are sodium sulphite, sodium hydrogen sulphite, sodium metabisulphite, ascorbic acid, ascorbylpalmitate, -myristate, -stearate, gallic acid, gallic acid alkyl ester, butylhydroxyamisol, nordihydroguaiaretic acid, tocopherols as well as synergists (substances which bind heavy metals through complex formation, for example lecithin, ascorbic acid, phosphoric acid ethylene diamine tetracetic acid, citrates, tartrates). Addition of synergists substantially increases the antioxygenic effect of the antioxidants.

Preservatives also be used in the oral dosage forms. Examples of preservatives include sorbic acid, p-hydroxybenzoic acid esters (for example lower alkyl esters), benzoic acid, sodium benzoate, trichloroisobutyl alcohol, phenol, cresol, benzethonium chloride, chlorhexidine and formalin derivatives.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active drug doses.

Pharmaceutically preparations of anti-ADA agents which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the anti-ADA agent in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium sterate and, optionally, stabilizers. In soft capsules, the anti-ADA agent may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosage suitable for such administration.

For buccal administration, the anti-ADA agent may take the form of tablets or lozenges formulation in conventional manner.

For administration by inhalation, anti-ADA agents of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or from propellant-free, dry-powder inhalers. In the

case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and suitable powder base such as lactose or starch.

In another variation of the embodiment, the anti-ADA agent is administrated parenterally, e.g. by bolus injection or continuous infusion. Formulations of anti-ADA agent for injection may be presented in unit dosage form, such as in ampules or in multidose containers, with an added preservative. The formulations may take such forms as suspension, solutions or emulsion in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for anti-ADA agents for parenteral administration include aqueous solutions of the anti-ADA agent in water-soluble form. Additionally, suspensions of the anti-ADA agent may be prepared as appropriate oily injection suspension. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable solubilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Examples of such solubilizers include, but are not limited to, cyclodextrin such as α-, β-, and γ-cyclodextrin and modified, amorphous cyclodextrin such as hydroxy-substituted α-, β–, and γ–cyclodextrin. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The anti-ADA agents may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter, carbowaxes, polyethylene glycols or other glycerides, all of which melt at body temperature, yet are solidified at room temperature.

In addition, the anti-ADA agents may be formulated as a depot preparation for administration by implantation (e.g., subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the anti-ADA agent may be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivative, for example, as sparingly soluble salt.

Alternatively, anti-ADA agents can be administrated to a patient with an autoimmune disease by employing other delivering systems such as liposome-mediated drug delivery. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the anti-ADA agents can be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the anti-ADA agent. Various types of sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the anti-ADA agent for a few weeks up to over 100 days.

In addition, the anti-ADA agents may be administrated in a targeted drug delivery system, for example, in a liposome coated with a cell-specific antibody. Such liposomes will be targeted to and taken up selectively by the cell of interest (a specific subset of T cells). Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. For example, long-circulating, i.e.,

stealth, liposomes can be employed. Such liposomes are generally described in US Patent No. 5,013,556, the teaching of which are hereby incorporated by reference.

Alternatively, the anti-ADA agents may also be administrated with various agents to reduce acid concentration in the stomach. This reduces acid lability and allows for enhanced concentrations of anti-ADA agents for enhanced gastric and/or intestinal absorption. For example, the anti-ADA agent may be coadministered with a H2 inhibitor such as cimetidine, an acid neutralizer.

The method of the present invention includes administrating to a subject in need thereof (e.g a patient or animal with an autoimmune disease) an anti-ADA agent composition wherein the anti-ADA agent is contained in a therapeutically effective amount. The amount of composition administered will, of course, dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgement of the prescribing physician. Determination of an effective amount is well within the capability of those skilled in the art, especially in the light of the detailed disclosure provided herein.

In a preferred embodiment, the method comprises administrating pentostatin to the patient.

According to this embodiment, pentostatin may be orally administrated to a patient with an autoimmune in need thereof in the form of a tablet. The patient may also be pretreated with an H2 blocker such as cimetidine to enhance the bioavailability of pentostatin.

Alternatively, pentostatin may be parenterally administrated to a patient carry an autoimmune disease. For example, pentostatin may be administered intravenously in 50 cc. 0.9 Normal Saline (NS) over a 30 minute period, together with intravenous hydration of 500 cc of 0.9 NS over 1 hour before and after pentostatin. In a preferable embodiment, a

pentostatin containing solution includes pentostatin in an amount of about 0.02 to about 1 weight percent, more preferably about 0.1 to about 0.3 weight percent, where the weight is based on the total compositional weight. Furthermore, the solution may contain additional ingredients, such as conventional pharmaceutical excipients. In a preferred embodiment, the pentostatin solution additionally comprises mannitol, and sterile water. Sodium hydroxide or hydrochloric acid may also be added to adjust pH.

Pentostatin as an inhibitor of adenosine deaminase may be synergized in inhibiting T lymphocytes by the administration of deoxyadenosine. In another preferred embodiment, pentostatin and may be coadministered with deoxyadenosine.

The method can be used to treat patients suffering from autoimmune diseases. The method is preferred to be used to treat those patients diagnosed with an autoimmune disease and tested having elevated levels of the T cell activation marker CD26. Patients include, but are not limited to those with multiple sclerosis, Graves' disease, systemic lupus erythematosus, diabetes mellitus, aseptic meningitus, systemic scleroderma, adult-onset idiopathic hypoparathyroidism and membranous glomerulonephritis.

For example, an adult patient who suffers from systemic lupus erythematosus and is HIV negative may be treated with an ADA inhibitor such as pentostatin. Pentostatin (e.g., NIPENT® supplied by SuperGen, Inc, San Ramon, CA) may be administered to the patient intravenously at 1-20 mg/m^2, preferably at 2-10 mg/m^2, and more preferably at 4-6 mg/m^2. The dosing schedule may be once a month or more frequent depending on the prognosis of the patient.

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, methods, and kits of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method for treating an autoimmune disease comprising administrating to a patient suffering from an autoimmune disease in need thereof a therapeutically effective amount of an anti-ADA agent.

2. A method according to claim 1, wherein the anti-ADA agent inhibits enzymatic activity of ADA.

3. A method according to claim 1, wherein the anti-ADA agent inhibits the binding of ADA to CD26.

4. The method according to claim 1, wherein the anti-ADA agent is selected from the group consisting of pentostatin, fludarabine monophosphate, 2-chloro-2'-deoxyadenosine, 2'-deoxyadenosine, 3'-deoxyadenosine and dideoxyadenosine.

5. The method according to claim 1, wherein the anti-ADA agent is administrated intravenously, intramuscularly, orally, by inhalation, parenterally, intraperitoneally, intraarterially, transdermally, sublingually, nasally, through use of suppositories, transbuccally, liposomally, adiposally, intraocularly, subcutaneously, intraarticularly, intrathecally, topically, or through local administration.

6. The method according to claim 1, wherein the anti-ADA agent is coadministered with an anti-autoimmune disease drug selected from the group consisting of cyclosporin A, methotrexate, cyclophosphamide, azathioprine and steroids.

7. The method according to claim 1, wherein the anti-ADA agent is coadministered with an anti-acid drug.

8. The method according to claim 1, wherein the anti-ADA agent is pentostatin.

9. The method according to claim 8, wherein pentostatin is administrated orally.

10. The method according to claim 9, wherein pentostatin is administrated orally in the form of a tablet.

11. The method according to claim 8, wherein pentostatin is administrated parenterally.

12. The method according to claim 11, wherein pentostatin is present in a solution comprising pentostatin.

13. The method according to claim 11, wherein the pentostatin is present in a solution that additionally comprises mannitol and sterile water.

14. The method according to claim 1, wherein the autoimmune disease is selected from the group consisting of multiple sclerosis, Graves' disease, systemic lupus erythematosus, diabetes mellitus, aseptic meningitus, systemic scleroderma, adult-onset idiopathic hypoparathyroidism and membranous glomerulonephritis.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 00/20081

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7076 A61K31/7056 A61K45/06 A61P37/00 A61P37/06 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data, CANCERLIT, AIDSLINE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ALBERT D A ET AL: "DEOXYCOFORMYCIN (PENTOSTATIN) FOR THE TREATMENT OF RHEUMATOID ARTHRITIS" JOURNAL OF INVESTIGATIVE MEDICINE,AMERICAN FEDERATION FOR CLINICAL RESEARCH,,US, vol. 44, no. 3, 1996, page 330A XP000949332 ISSN: 1081-5589	1-6,8, 11,12
Y	the whole document	1,7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document 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	Date of mailing of the international search report
15 December 2000	22/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, E

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/US 00/20081

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 17809 A (GENSIA INC) 18 August 1994 (1994-08-18)	1-5, 8-12,14
Y	abstract page 1, line 1 - line 8 page 5, line 21 - line 23 page 8, line 6 - line 30 page 9, line 9 - line 18 page 12, line 10 - line 24 page 18, line 14 -page 19, line 37 claims 24-26,33-38	1,7

X	WO 94 09791 A (SCHERING AG) 11 May 1994 (1994-05-11)	1-5,14
Y	abstract page 1, line 4 - line 9 page 4, line 34 -page 5, line 8 page 6, line 29 -page 7, line 2 page 8, line 9 - line 35 claims	1,7

X	WO 98 18430 A (UNIV NORTH CAROLINA ;BOYER JOSE L (US); CAMAIONI EMIDIO (US); HARD) 7 May 1998 (1998-05-07)	1-5,14
Y	page 3, line 1 -page 4, line 11 page 5, line 12 - line 18 table 1 page 15, line 19 - line 27 page 16, line 8 - line 10 page 27, line 20 - line 26 page 28, line 5 - line 11 page 31, line 6 - line 20	1,7

X	W.D. KLOHS AND A.J. KRAKER: "Pentostatin: Future directions" PHARMACOLOGICAL REVIEWS, vol. 44, no. 4, December 1992 (1992-12), pages 459-473, XP000965615 page 460, column 1, paragraph 3 -column 2, paragraph 1 page 469, column 2, paragraph 4 page 471, column 1, paragraph 4 page 473, column 2, paragraph 3 - paragraph 4	1-6,8,14

	-/--	

2

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 00/20081

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	THLIVERIS JAMES A ET AL: "Prevention of insulin-dependent diabetes mellitus by 2'-deoxycoformycin in the BB Wistar rat." BIOCHEMICAL PHARMACOLOGY, vol. 46, no. 6, 1993, pages 1071-1075, XP000965635 ISSN: 0006-2952 abstract page 1071, column 2, paragraph 2 page 1072, column 2, paragraph 2 figure 1 page 1074, column 1, paragraph 2 page 1074, column 2, paragraph 2 ---	1-5,8, 11,14
X	BLANCHE PHILIPPE ET AL: "Scleroderma, polymyositis, and hairy cell leukemia." JOURNAL OF RHEUMATOLOGY, vol. 22, no. 7, 1995, pages 1384-1385, XP000965634 ISSN: 0315-162X page 1384, column 1, paragraph 1 page 1384, column 2, paragraph 1 page 1385, column 1, paragraph 2 ---	1-4,6,8, 14
X	US 5 506 214 A (BEUTLER ERNEST) 9 April 1996 (1996-04-09)	1-5,14
Y	abstract column 4, line 20 -column 5, line 17 column 8, line 13 - line 48 column 9, line 62 -column 10, line 2 examples 1,2 claims ---	1,7
X	US 5 401 724 A (BEUTLER ERNEST) 28 March 1995 (1995-03-28)	1-5,7,14
Y	abstract column 2, line 39 - line 52 column 3, line 48 - line 55 column 7, line 57 - line 63 column 9, line 3 - line 20 example 3 ---	1,7
X	US 4 400 387 A (ROSSEELS GILBERT ET AL) 23 August 1983 (1983-08-23)	1-3,5,14
Y	abstract column 1, line 45 - line 55 column 8, line 64 -column 9, line 5 column 11, line 17 - line 61 example 14 --- -/--	1,7

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MAJEWSKI SLAWOMIR ET AL: "Systemic administration of 2-chloro-2'-deoxyadenosine (2-CdA) in patients with systemic scleroderma." ARCHIVUM IMMUNOLOGIAE ET THERAPIAE EXPERIMENTALIS, vol. 42, no. 1, 1994, pages 33-34, XP000972009 ISSN: 0004-069X the whole document ---	1-5,14
X	DAVIS JOHN C JR ET AL: "A pilot study of 2-chloro-2'-deoxyadenosine in the treatment of systemic lupus erythematosus-associated glomerulonephritis." ARTHRITIS & RHEUMATISM, vol. 41, no. 2, February 1998 (1998-02), pages 335-343, XP000972123 ISSN: 0004-3591 abstract page 336, column 1, paragraph 2 page 340, column 2, paragraph 3 -page 341, column 2, paragraph 1 page 342, column 1, paragraph 4 -column 2, paragraph 1 ---	1-6,14
P,X	WO 00 25758 A (WRENN SIMEON M JR ;SUPERGEN INC (US)) 11 May 2000 (2000-05-11) abstract page 1, line 15 - line 24 page 4, line 16 - line 27 page 5, line 26 -page 6, line 2 page 8, line 16 - line 20 page 10, line 17 - line 28 page 11, line 16 - line 21 page 14, line 5 - line 11 page 29, line 13 - line 22 examples 1-7 claims 1,27,30,31 ---	1-5,7-12
P,X	WO 99 62525 A (ALBERT DANIEL A ;SUPERGEN INC (US)) 9 December 1999 (1999-12-09) abstract page 5, line 13 -page 7, line 5 page 9, line 5 - line 10 page 15, line 3 -page 16, line 17 examples 1,2 claims 1-8,13 -----	1-13

2

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3, 5-7, 14 relate to a therapeutic method using a compound defined by reference to a desirable characteristic or property, namely "an anti-ADA agent".
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Moreover, present claim 7 relates to a therapeutic method using a compound which actually is not well defined. The use of the definition "an anti-acid drug" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. The lack of clarity is such as to render a meaningful complete search impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds specifically mentioned in claims 4, 8-13 and the anti-acid drug cimetidine, as disclosed in the description (p.13, lines 4-9).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/US 00/20081

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9417809 A	18-08-1994	AU 6297294 A	29-08-1994
WO 9409791 A	11-05-1994	EP 0665753 A	09-08-1995
		JP 8502751 T	26-03-1996
WO 9818430 A	07-05-1998	AU 5584698 A	22-05-1998
		CA 2241687 A	07-05-1998
		EP 0929218 A	21-07-1999
US 5506214 A	09-04-1996	US 5310732 A	10-05-1994
		US 5106837 A	21-04-1992
		AT 192045 T	15-05-2000
		AU 682818 B	23-10-1997
		AU 3724993 A	13-09-1993
		BR 9305907 A	21-10-1997
		CA 2130275 A	02-09-1993
		CH 684310 A	31-08-1994
		DE 69328474 D	31-05-2000
		DE 69328474 T	28-09-2000
		EP 0626853 A	07-12-1994
		FI 943805 A	19-10-1994
		HU 68030 A	29-05-1995
		JP 2688113 B	08-12-1997
		JP 7507540 T	24-08-1995
		NO 942765 A	13-09-1994
		NO 20000762 A	13-09-1994
		RU 2130308 C	20-05-1999
		WO 9316706 A	02-09-1993
		US 5541164 A	30-07-1996
		US 5506213 A	09-04-1996
		AT 128141 T	15-10-1995
		AU 626296 B	30-07-1992
		AU 3410589 A	05-10-1989
		CA 1339964 A	21-07-1998
		DE 68924319 D	26-10-1995
		DE 68924319 T	15-05-1996
		DK 572189 A	15-11-1989
		EP 0364559 A	25-04-1990
		JP 3501258 T	22-03-1991
		JP 3090456 B	18-09-2000
		KR 138996 B	30-04-1998
		NO 894558 A	15-11-1989
		WO 8908658 A	21-09-1989
US 5401724 A	28-03-1995	AU 678557 B	05-06-1997
		AU 4377293 A	13-12-1993
		EP 0642347 A	15-03-1995
		JP 7507775 T	31-08-1995
		WO 9323058 A	25-11-1993
US 4400387 A	23-08-1983	AR 225314 A	15-03-1982
		AT 375078 B	25-06-1984
		AT 354380 A	15-11-1983
		AU 529725 B	16-06-1983
		AU 5948780 A	15-01-1981
		CA 1153379 A	06-09-1983
		DD 151940 A	11-11-1981
		DE 3060097 D	28-01-1982

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 00/20081

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4400387 A		DK 291180 A,B,	07-01-1981
		EP 0022762 A	21-01-1981
		ES 493139 D	16-06-1981
		ES 8105710 A	01-09-1981
		FI 802165 A,B,	07-01-1981
		GB 2051812 A	21-01-1981
		GR 69280 A	13-05-1982
		HU 182151 B	28-12-1983
		IE 49994 B	22-01-1986
		IN 151594 A	04-06-1983
		JP 56018979 A	23-02-1981
		MX 6744 E	20-06-1986
		NO 802015 A,B,	07-01-1981
		NZ 193926 A	31-05-1984
		OA 6563 A	31-07-1981
		PL 225479 A	30-10-1981
		PT 71424 A	01-07-1980
		SU 993817 A	30-01-1983
		YU 171880 A	31-10-1983
		ZA 8003434 A	27-05-1981
WO 0025758 A	11-05-2000	AU 1711000 A	22-05-2000
WO 9962525 A	09-12-1999	AU 4322099 A	20-12-1999