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(54) Benævnelse: **Fremgangsmåde til reduktion og behandling af UVB-induceret immunsuppression**

(56) Fremdragne publikationer:
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WO-A-98/48805
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DESCRIPTION

Background of the Invention

[0001] Human skin is an organ that protects the body from the influences of the external environment. A portion of that protective function is provided by an immune system specific to the skin - the so-called skin immune system - that protects the body from potentially harmful environmental influences including pathogens and transformed skin cells. The skin immune system may provide a localized response known as contact hypersensitivity (CHS), a systemic response known as delayed type hypersensitivity (DTH), or both.

[0002] Exposing skin to ultraviolet radiation of the sun, particularly UV-B radiation, may damage certain types of cells involved in the skin immune system. Such damage may at least partially suppress function of the skin immune system and, therefore, may result in UV-induced immunosuppression.

[0003] Langerhans cells are dendritic-like elements of the skin immune system that may function to present antigens to Th1-lymphocytes. Langerhans cells may be particularly affected by exposure to UV radiation. Exposure to UV radiation can cause changes in Langerhans cells that may contribute to UV-induced immunosuppression. For example, exposure to UV radiation may impair the ability of Langerhans cells to present antigens.

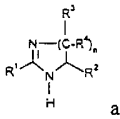
[0004] Cytokines are known to be involved in the development of contact hypersensitivity (CHS) and the suppression of contact hypersensitivity by UV radiation. For example, interleukin (IL)-10 is a cytokine produced by keratinocytes after the keratinocytes are exposed to UV radiation. IL-10 impairs Langerhans cell function and suppresses CHS. Also, IL-12 promotes a Th1-lymphocyte immune response and is involved in the induction of CHS. IL-12 can reduce the immunosuppressive effects of UV radiation. Furthermore, administration of IL-12 prior to UV treatment may counteract UV-induced systemic suppression of delayed type hypersensitivity (DTH).

[0005] Ectoin and ectoin derivatives may be used for the prophylaxis or treatment of UV-induced immunosuppression. Such compounds may be incorporated into compositions for topical administration.

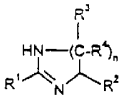
[0006] WO-A-01/15698 describes a method for the treatment of topical sarcoidosis on equine, comprising the steps of providing a therapeutic substance comprising a therapeutically effective amount of imiquimod, and applying the therapeutic substance at least once to an outer surface of the body of an equine.

[0007] JP-A-2000 247884 describes a treating agent of arachidonic acid-induced skin diseases which contains an imiquimod or its acid adducts salt as an active ingredient.

[0008] WO-A-01/72287 describes the use of at least one compound selected from



and



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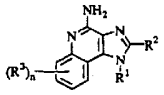
a physiologically compatible salt thereof or a stereoisomeric form thereof, for the prophylaxis and/or treatment of UV-induced immunosuppression, wherein these compounds are generally utilized in the form of a topical composition.

[0009] WO-A-01/52808 describes methods for the treatment or prevention of UV-induced immunosuppression, skin erythema and skin collagen damage which involve the administration of carnosine, acycarnosine or related compounds.

[0010] WO-A-99/36050 describes a method for protecting skin from either UV-induced immunosuppression or from UV-induced skin damage, comprising the topical administration of a composition containing an extract of soy or clover, and/or the isoflavone compounds genistein, biochanin, dihydro-daidzein, diadzein, formonentin, dihydro-geneistein, 2-dehydro-O-desmethyl-angolensin, tetrahydro-daidzein, equol, dehydro-equol, O-desmethyl-angolensin, or 6-hydroxy-O-desmethyl-angolensin.

[0011] WO-A-98/48805 describes a pharmaceutical composition for suppressing Th2 type immune response comprising as active ingredient a compound represented by formula



or a pharmaceutically acceptable acid salt thereof, and a method for treating or preventing a disease caused by abnormal activation of Th2 type immune response, such as asthma, allergic dermatitis, allergic rhinitis or systemic lupus erythematosus, comprising administering a therapeutically effective amount of the compound.

[0012] Further uses of imiquimod are described in:

- Hirotake Suzuki et al., "Imiquimod, a topical immune response modifier, induces migration of Langerhals cells", THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, Vol. 114, No. 1 January 2000, pages 135-141;
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- C.J. Harrison et al., "Effects of cytokines and R-837, a cytokine inducer, on UV-irradiation augmented recurrent genital herpes in guinea pigs", ANTIVIRAL RESEARCH, Vol. 15, 1991, pages 315-322; and
- K.R. Beutner et al., "Therapeutic response of basal cell carcinoma to the immune response modifier imiquimod 5% cream", JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, Vol. 41, No. 6, December 1999, pages 1002-1007.

Summary of the Invention

[0013] The present invention relates to an immune response modifier compound for use in reducing UV-induced immunosuppression which use comprises administering to a treatment area said immune response modifier compound in an amount effective to inhibit UV-induced immunosuppression, wherein the immune response modifier compound is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (imiquimod), wherein administration of the immune response modifier compound occurs prior to exposure of the treatment area to UV irradiation, and wherein the immune response modifier compound is administered via a sunscreen.

[0014] Herein also described is a method of reducing UV-induced immunosuppression that includes administering to a treatment area an immune response modifier compound in an amount effective to inhibit UV-induced immunosuppression.

[0015] In certain embodiments described herein, the immune response modifier compound can be an agonist of at least one Toll-like receptor (TLR). For example, in some embodiments described herein, the immune response modifier compound can include an imidazoquinoline amine, an imidazopyridine amine, a 6,7-fused cycloalkylimidazopyridine amine, a 1,2-bridged imidazoquinoline amine, an imidazonaphthyridine amine, an oxazoloquinoline amine, an imidazotetrahydronaphthyridine amine, a thiazoloquinoline amine, an oxazolopyridine amine, a thiazolopyridine amine, an oxazolonaphthyridine amine, or a thiazolonaphthyridine amine. In certain embodiments, the immune response modifier compound is administered via a topical application vehicle such as a cream, a gel, a spray, an ointment, a lotion, a solution, a suspension, an emulsion, a paste, a powder, or an oil.

[0016] Herein also described is a method of treating UV-induced immunosuppression that includes administering to a treatment area an immune response modifier compound in an amount effective to inhibit UV-induced immunosuppression. In certain embodiments, the immune response modifier compound can be an agonist of at least one Toll-like receptor (TLR). For example, in some embodiments described herein, the immune response modifier compound can include an imidazoquinoline amine, an imidazopyridine amine, a 6,7-fused cycloalkylimidazopyridine amine, a 1,2-bridged imidazoquinoline amine, an imidazonaphthyridine amine, an imidazotetrahydronaphthyridine amine, an oxazoloquinoline amine, a thiazoloquinoline amine, an oxazolopyridine amine, a thiazolopyridine amine, an oxazolonaphthyridine amine, or a thiazolonaphthyridine amine.

[0017] In certain embodiments, the immune response modifier compound is administered via a topical application vehicle such as a cream, a gel, a spray, an ointment, a lotion, a solution, a suspension, an emulsion, a paste, a powder, or an oil.

[0018] Various other features and advantages of the present invention should become readily apparent with reference to the following detailed description, examples, claims and appended drawings. In several places throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group and should not be

interpreted as an exclusive list.

Brief Description of the Drawings

[0019]

Fig. 1 is a summary of the protocol for testing the contact hypersensitivity of mice treated with IRM before exposure to UV-B radiation;

Fig. 2 is a bar graph summarizing the contact hypersensitivity of mice treated with IRM before exposure to UV-B radiation;

Fig. 3 is a summary of the protocol for testing the contact hypersensitivity of mice treated with IRM after exposure to UV-B radiation;

Fig. 4 is a bar graph summarizing the contact hypersensitivity of mice treated with IRM after exposure to UV-B radiation.

Detailed Description of Illustrative Embodiments of the Invention

[0020] The present invention relates to an immune response modifier compound for use in reducing UV-induced immunosuppression, as described in the claims.

[0021] Immune response modifiers ("IRMs") include compounds that possess potent immunostimulating activity including but not limited to antiviral and antitumor activity. Certain IRMs effect their immunostimulatory activity by inducing the production and secretion of cytokines such as, e.g., Type I interferons, TNF-α, IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and MCP-1. Certain IRMs are small organic molecules such as those disclosed in, for example, U.S. Patent Nos. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,352,784; 5,389,640; 5,482,936; 5,494,916; 6,110,929; 6,194,425; 4,988,815; 5,175,296; 5,367,076; 5,395,937; 5,693,811; 5,741,908; 5,238,944; 5,939,090; 6,039,969; 6,083,505; 6,245,776; 6,331,539; and 6,376,669; and PCT Publications WO 00/76505; WO 00/76518; WO 02/46188, WO 02/ 46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; and WO 02/46194.

[0022] Additional small molecule IRMs include purine derivatives (such as those described in U.S. Patent Nos. 6,376,501 and 6,028,076), small heterocyclic compounds (such as those described in U.S. Patent No. 6,329,381), and amide derivatives (such as those described in U.S. Patent No. 6,069,149).

[0023] Other IRMs include large biological molecules such as oligonucleotide sequences. Some IRM oligonucleotide sequences contain cytosine-guanine dinucleotides (CpG) and are described, for example, in U.S. Patent Nos. 6,1994,388; 6,207,646; 6,239,116; 6,339,068; and 6,406,705. Some CpG-containing oligonucleotides can include synthetic immunomodulatory structural motifs such as those described, for example, in U.S. Pat. Nos. 6,426,334 and 6,476,000. Other IRM nucleotide sequences lack CpG and are described, for example, in PCT Publication No. WO 00/75304.

[0024] Certain IRMs can function as Toll-like receptor (TLR) agonists, i.e., their immunomodulating influence is exerted through a TLR-mediated cellular pathway. For example, some small molecule IRMs have been identified as agonists of one or more of TLRs 2, 4, 6, 7, and 8; and CpG has been identified as an agonist of TLR 9. In many cases, activating a TLR-mediated pathway results in gene transcription (e.g., cytokine or co-stimulatory marker expression) by activating NF-κB regardless of the particular TLR that is activated.

[0025] Certain IRM compounds may be useful for the treatment of Th2-mediated diseases because they inhibit the Th2 immune response, suppress IL-4/IL-5 cytokine induction and eosinophilia, and enhance Th1 immune response. IRM compounds that act as an agonist of at least one TLR have been shown to be particularly useful in this regard. Some IRM compounds have been found to have pharmacological effects on Langerhans cells as well. Human Langerhans cells are known to be derived from myeloid dendritic cells that express TLR8.

[0026] Therefore, described herein are methods of reducing (including preventing) and/or treating UV-induced immunosuppression by administering one or more IRM compounds. In certain embodiments described herein, UV-induced immunosuppression may be reduced by prophylactic administration of an IRM compound to a portion of the skin (e.g., topical

application) before the skin is exposed to UV radiation. In an embodiment herein also described, UV-induced immunosuppression may be therapeutically treated by administration of an IRM compound to a portion of the skin (e.g., topical application) that has already been exposed to UV radiation. In yet other embodiments herein also described, prophylactically reducing or therapeutically treating UV-induced immunosuppression may be accomplished by administering one or more IRM compounds systemically.

[0027] In certain embodiments described herein, the IRM compound includes an agonist of at least one TLR. In particular embodiments, the IRM compound can be an agonist of TLR7, TLR8, or TLR9. For example, the IRM compound can be an imidazopyridine amine, a 6,7-fused cycloalkylimidazopyridine amine, a 1,2-bridged imidazoquinoline amine, an imidazonaphthyridine amine, an imidazotetrahydronaphthyridine amine, an oxazoloquinoline amine, a thiazoloquinoline amine, an oxazolopyridine amine, a thiazolopyridine amine, an oxazolonaphthyridine amine, a thiazolonaphthyridine amine, or an imidazoquinoline amines including but not limited to 4-amino-2-ethoxymethyl-α,α-dimethyl-1H-imidazo[4,5-c]quinolin-1-ethanol, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine, a 1,2-bridged imidazoquinoline amine, a sulfonamido-substituted imidazoquinoline amine; a urea-substituted imidazoquinoline amine; or a heteroaryl ether-substituted imidazoquinoline amine. The IRM may induce the production of one or more cytokines including but not limited to Type I interferons. In the present invention, the immune response modifier compound is 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

[0028] The IRM compound may be incorporated into a composition for topical administration. Suitable types of compositions include, but are not limited to, ointments, gels, foams, creams, lotions, solutions, suspensions, emulsions, pastes, powders, soaps, surfactant-containing cleaning preparations, solid sticks (e.g., wax- or petroleum-based sticks), oils and sprays. In particular exemplary embodiments described herein, the IRM compound may be incorporated into, for example, a sunscreen, a skin lotion, a skin moisturizer, or cosmetic.

[0029] Alternatively, the IRM compound may be incorporated into any vehicle suitable for systemic delivery. Typical systemic delivery routes include but are not limited to injection (e.g., intravenous, subcutaneous, intraperitoneal, intradermal), inhalation, ingestion, transdermal, or transmucosal delivery.

[0030] The particular amount of IRM compound necessary to (1) prophylactically reduce or prevent, or (2) therapeutically treat UV-induced immunosuppression in a subject may depend, at least in part, on one or more factors. Such factors include but are not limited to the particular IRM compound being administered, the state of the subject's immune system (e.g., suppressed, compromised, stimulated); the subject's past and expected UV exposure; the route of administering the IRM; and the desired result (i.e., prophylactic reduction or prevention, or therapeutic treatment). Accordingly it is not practical to set forth generally the amount that constitutes an effective amount of IRM compound. Those of ordinary skill in the art, however, can readily determine the appropriate amount with due consideration of such factors.

Examples

[0031] The following examples have been selected merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention. Unless otherwise indicated, all percentages and ratios are by weight.

Example 1 - Contact Hypersensitivity in Mice Treated with IRM Before Exposure to UV-B Radiation

[0032] Figure 1 summarizes the protocol used for testing the contact hypersensitivity of mice treated with immune response modifier compound 1-(2-methylpropyl)-1H imidazo[4,5-c]quinolin-4-amine (IRM) before exposure to UV-B radiation.

[0033] A topical cream including either a) 5% IRM (treated), or b) no IRM (vehicle-treated) was applied to a shaved portion of the abdomen of UVB-susceptible C57BL6 mice. The cream was applied for two consecutive days beginning five days before sensitization (Day -5 and Day -4).

[0034] The mice were exposed to either a) UV-B radiation, 70 mJ/cm from FS-20 light bulbs (National Biological Corp., Twinsburg, OH) equipped with a cellulose acetate filter to provide predominantly UV-B output, or b) sham radiation for four consecutive days beginning at three days prior to sensitization (Day -3 through Day 0).

[0035] The mice were sensitized for two consecutive days beginning at Day 0 (Day 0 and Day 1) with 25 µL of 0.5% dinitrofluorobenzene (DNFB, Sigma Chemical Co., St. Louis, MO) applied to the shaved portion of the abdomen.

[0036] On Day 5 after sensitization, the mice were challenged with DNFB on the pinna of the ear.

[0037] On Day 6 after sensitization, the extent to which the thickness of the ear pinna changed was measured in both the treated and untreated mice.

[0038] Three experiments were performed according to the protocol summarized in Figure 1. The results of each of the three experiments and the average of all three experiments are provided in Figure 2.

Example 2 - Contact Hypersensitivity in Mice Treated with IRM After Exposure to UV-B Radiation

[0039] Figure 3 summarizes the protocol used for testing the contact hypersensitivity of mice treated with immune response modifier compound 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine (IRM) after exposure to UV-B radiation.

[0040] The mice were exposed to either a) UV-B radiation, 70 mJ/cm from FS-20 light bulbs (National Biological Corp., Twinsburg, OH) equipped with a cellulose acetate filter to provide predominantly UV-B output, or b) sham radiation for four consecutive days beginning at four days prior to sensitization (Day -4 through Day -1).

[0041] A topical cream including either a) 5% IRM (treated), or b) no IRM (vehicle-treated) was applied to a shaved portion of the abdomen of UVB-susceptible C57BL6 mice. The cream was applied for two consecutive days beginning one day before sensitization (Day -1 and Day 0).

[0042] The mice were sensitized for two consecutive days beginning at Day 0 (Day 0 and Day 1) with 25 µL of 0.5% dinitrofluorobenzene (DNFB, Sigma Chemical Co., St. Louis, MO) applied to the shaved portion of the abdomen.

[0043] On Day 5 after sensitization, the mice were challenged with DNFB on the pinna of the ear.

[0044] On Day 6 after sensitization, the extent to which the thickness of the ear pinna changed was measured in both the treated and untreated mice.

[0045] Two experiments were performed according to the protocol summarized in Figure 3. The results of those two experiments are shown in Figure 4.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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Patentkrav

1. Immunrespons-modificerende forbindelse til anvendelse ved reduktion af UV-induceret immunsuppression, hvilken anvendelse omfatter tilførsel til et behandlingsområde af den immunrespons-modificerende forbindelse i en mængde, der er virksom til inhibering af UV-induceret immunsuppression, hvor den immunrespons-modificerende forbindelse er 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amin, hvor tilførslen af den immunrespons-modificerende forbindelse finder sted inden udsættelse af behandlingsområdet for UV-stråling, og hvor den immunrespons-modificerende forbindelse tilføres via et solbeskyttelsesmiddel.

2. Immunrespons-modificerende forbindelse til anvendelse ifølge krav 1, hvor det topiske tilførselsmedium omfatter en creme, en gel, en spray, en salve, en lotion, en opløsning, en suspension, en emulsion, en pasta, et pulver eller en olie.

DRAWINGS

FIG. 1

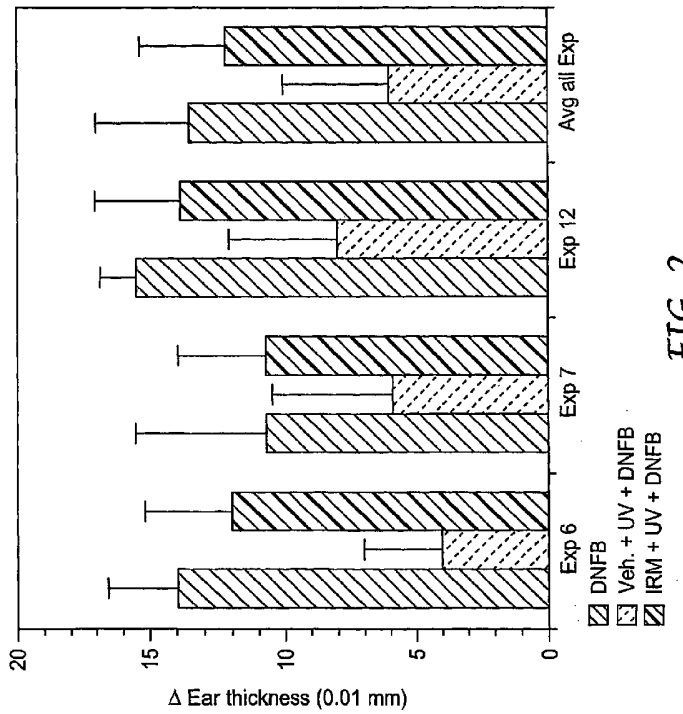
Δ Ear thickness (0.01 mm)
0
5
10
15
20
Exp 6
Exp 7
Exp 12
Avg all Exp
DNFB
Veh. + UV + DNFB
IRM + UV + DNFB

FIG. 2

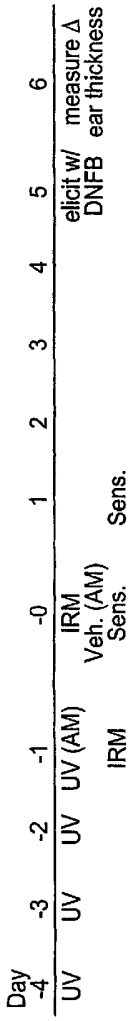
Day
-4
-3
-2
-1
-0
1
2
3
4
5
6
UV
UV
UV
UV (AM)
IRM
Veh. (PM)
IRM
Veh. (AM)
Sens.
DNFB (PM)
Sens.
DNFB
elicit w/
DNFB
measure Δ
ear thickness

FIG. 3

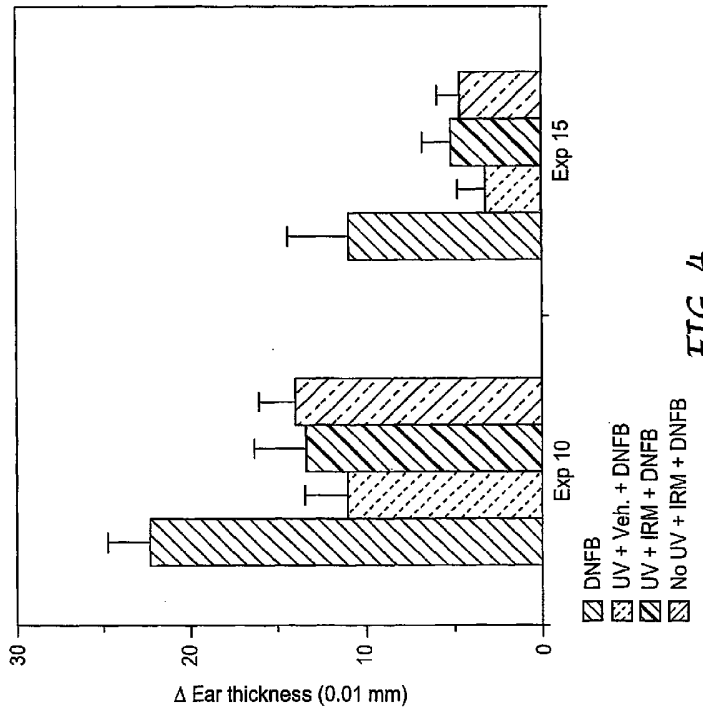
Δ Ear thickness (0.01 mm)
30
20
10
0
Exp 10
Exp 15
DNFB
UV + Veh. + DNFB
UV + IRM + DNFB
No UV + IRM + DNFB

FIG. 4