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(71) Applicant: **SCARCELL THERAPEUTICS** [FR/FR]; 101 rue de Sèvres, 75279 Paris Cedex 06 (FR).

(72) Inventors: **LAFONT, Antoine**; 46 rue du Bac, F-75007 Paris (FR). **COULOMB, Bernard**; 46 avenue de la République, F-91430 Igny (FR).

(74) Agent: **VIAL, Lionel**; Cabinet Lionel Vial, 6 rue de Vaugondran, 91190 Gif sur Yvette (FR).

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(54) Title: COMPOSITIONS USEFUL FOR THE TREATMENT OF IMMUNE-RELATED DISEASES

(57) Abstract: The present invention relates to a gingival fibroblast-derived product for use in the treatment or prevention of an immune-related disease in an individual.

COMPOSITIONS USEFUL FOR THE TREATMENT OF IMMUNE-RELATED DISEASES

Field of the invention

The present invention relates to compounds and compositions useful for the treatment of immune-related diseases, in particular for the treatment of atopic dermatitis, in an individual.

Background of the invention

Immune-related diseases represent an important part of debilitating diseases in humans. Indeed, these diseases notably encompass autoimmune diseases, inflammatory diseases, in particular inflammatory skin diseases, and allergic diseases, including dermatitis, atopic dermatitis, inflammatory skin rash, asthma and arthritis.

Although the aetiology of these conditions is unknown for the most part, immune-related diseases result from a dysregulation of the normal immune response. This immune dysregulation often involves the inappropriate activation of inflammatory cytokines, such as TSLP (Thymic stromal lymphopoietin) (Cianferoni *et al.* (2014) *Expert Rev. Clin. Immunol.* 10: 1463-1474) and CCL26 (Kagami *et al.* (2005) *Clinical and Experimental Immunology* 141:459-466; Sera *et al.* (2008) *An. Bras. Dermatol.* 83:57-73).

By way of example, atopic dermatitis, also known as eczema, is a multifactorial disease associated to an alteration of the epidermal barrier and a high sensitivity to allergens. It generally evolves by recurrent inflammatory flare-ups. The major symptoms of atopic dermatitis are skin dryness (xerosis), erythema, itching, and red plates. It generally starts in childhood and it is considered that 15 to 20% of infants suffer from atopic dermatitis in developed countries. The further development of this disease often leads to asthma in adolescents and allergic rhinitis in adults. In addition, the disease often leads to significant physical and psychological distress.

The usual pharmaceutical treatment of inflammatory skin diseases, such as atopic dermatitis, involves topical steroids, in particular dexamethasone (Hon *et al.* (2015), *Hong Kong Med. J.*, 21: 251-261.), which are used to reduce inflammation. In complement to topical steroids, daily care, e.g. soap-free cleansing lotions and moisturizers, is essential in particular for decreasing skin dryness. However, steroid-based treatments have several side effects, such as skin atrophy, and their effectivity decreases over time. In addition, they are generally poorly tolerated by the patients.

More generally, treatments currently available for atopic dermatitis are exclusively symptomatic and are unable to maintain a long-lasting remission.

Accordingly, there is a need for an alternative to these therapies, which would be effective to cure immune-related diseases in addition to treating the symptoms.

Summary of the invention

The present invention arises from the unexpected finding by the inventors that gingival fibroblast-conditioned medium can inhibit the secretion of inflammatory cytokines TSLP, CCL-26 and IL-1β by human keratinocytes (*i.e.* skin cells) submitted to inflammatory conditions.

Thus, the present invention relates to a gingival fibroblast-derived product for use in the treatment or prevention of an immune-related disease in an individual.

In an embodiment of the invention, the above-defined gingival fibroblast-derived product is associated with at least one agent intended for the prevention or treatment of inflammatory skin disease, in particular selected from the group consisting of a corticosteroid, a calcineurin inhibitor, an emollient and a moisturizer.

The invention also relates to a composition comprising a gingival fibroblast-derived product for use in the prevention or treatment of an immune related disease.

The invention also relates to a composition comprising a gingival fibroblast-derived product as defined above and further comprising at least one agent intended for the prevention or treatment of inflammatory skin disease and optionally comprising at least one pharmaceutically acceptable carrier or excipient, in particular for use in the prevention or treatment of an immune related disease.

The invention also relates to the non-therapeutic use of a gingival fibroblast-derived product for the cosmetic treatment of skin dryness of an individual, optionally associated with at least one cosmetic agent intended for the cosmetic treatment of skin dryness.

The invention also relates to a cosmetic composition comprising a gingival fibroblast-derived product and at least one cosmetic agent intended for the cosmetic treatment of skin dryness, and optionally at least one cosmetically acceptable carrier or excipient.

The invention also relates to a method for preventing or treating an inflammatory skin disease in an individual, comprising administering to the individual a

prophylactically or therapeutically effective amount of a gingival fibroblast-derived product.

The invention also relates to the above-defined method for preventing or treating an inflammatory skin disease further comprising administering to the individual at least one agent intended for the prevention or treatment of inflammatory skin disease, preferably selected from the group consisting of a corticosteroid, a calcineurin inhibitor, an emollient and a moisturizer.

The invention also relates to a method for the cosmetic treatment of skin dryness in an individual, comprising administering to the individual a cosmetically effective amount of a gingival fibroblast-derived product and optionally at least one cosmetic agent intended for the cosmetic treatment of skin dryness.

The invention also relates to a method for the cosmetic treatment of skin dryness in an individual, comprising administering to the individual a cosmetic composition comprising a gingival fibroblast-derived product and further comprising at least one cosmetic agent intended for the cosmetic treatment of skin dryness, and optionally at least one cosmetically acceptable carrier or excipient.

Detailed description of the invention

As intended herein, the term "comprising" has the meaning of "including" or "containing", which means that when an object "comprises" one or several elements, other elements than those mentioned may also be included in the object. In contrast, when an object is said to "consist of" one or several elements, the object is limited to the listed elements and cannot include other elements than those mentioned.

Immune-related disease

As intended herein, an "immune-related disease" refers to any disease which is linked or due to a dysfunction, in particular a dysregulation, such as an over-activation of the immune system.

The immune-related disease according the invention is preferably selected from the group consisting of an inflammatory disease, in particular a chronic inflammatory disease, an inflammatory skin disease, an auto-immune disease and an allergic disease. More preferably, the immune-related disease according to the invention is selected from the group consisting of an inflammatory skin disease, iritis and asthma.

Preferably, the inflammatory skin disease according to the invention is a chronic inflammatory skin disease. Preferably also the inflammatory skin disease according to the invention is selected from the group consisting of dermatitis, inflammatory skin rash, ichthyosis and psoriasis.

Preferably, the immune-related disease is dermatitis. Dermatitis refers to a group of pruritic chronic inflammatory skin diseases well known to the one of ordinary skill in the art and which are notably defined in classes L20 to L30 in the 10th revision of the International Classification of Diseases (ICD-10) 2016 version by the World Health Organization.

Dermatitis according to the invention is thus preferably selected form the group consisting of:

- Atopic dermatitis (e.g. L20 ICD-10),
- Seborrhoeic dermatitis (e.g. L21 ICD-10),
- Diaper dermatitis (e.g. L22 ICD-10),
- Allergic contact dermatitis (e.g. L23 ICD-10),
- Irritant contact dermatitis (e.g. L24 ICD-10),
- Unspecified contact dermatitis (e.g. L25 ICD-10),
- Exfoliative dermatitis (e.g. L26 ICD-10),
- Dermatitis due to substances taken internally (e.g. L27 ICD-10),
- Lichen simplex chronicus and prurigo (e.g. L28 ICD-10), and
- Pruritus (e.g. L29 ICD-10).

More preferably, the immune-related disease according to the invention is atopic dermatitis. As intended herein dermatitis is also named eczema.

The chronic inflammatory disease according to the invention is preferably selected from the group consisting of rheumatoid arthritis, lupus erythematosus and multiple sclerosis.

Inflammatory skin rash according to the invention is notably defined in class R21 of ICD-10. Ichthyosis according to the invention is notably defined in classes L85 and Q80 of ICD-10. Psoriasis according to the invention is notably defined in class L40 of ICD-10. Lupus erythematosus according to the invention is notably defined is class L93 of ICD-10. Asthma according to the invention is notably defined is class J45 of ICD-10. rheumatoid arthritis according to the invention is notably defined in class M06 of ICD-10. Iritis according to the invention is notably defined in class H19 of ICD-10. Multiple sclerosis according to the invention is notably defined in class G35 of ICD-10.

Individual

As intended herein, the "individual" according to the invention is preferably a mammal, more preferably a human, or a pet animal. Most preferably, the individual according to the invention is a human.

Preferably, the individual according to the invention is an infant, a child or an adolescent. Preferably also, the individual according to the invention is a human adult.

In an aspect of the invention, the individual according to the invention can have one or more symptoms of an immune-related disease.

In another aspect of the invention, the individual according to the invention does not suffer from an immune-related disease, in particular an inflammatory skin disease according of the invention. This may notably be the case in the frame of the non-therapeutic use or of the cosmetic treatment of skin dryness according to the invention.

Gingival fibroblast-derived product

As intended herein, "gingival fibroblast-derived product" relates to any product which can be obtained from gingival fibroblasts in themselves or which contains gingival fibroblasts secretions. The gingival fibroblast-derived product according to the invention is preferably selected form the group consisting of gingival fibroblast whole cells, a gingival fibroblast culture, a gingival fibroblast extract, and a gingival fibroblast conditioned medium.

Procedures for taking, culturing and preserving gingival fibroblasts are well known to one of ordinary skill in the art and are particularly described in Naveau *et al.* (2006) *J. Periodontol.* 77:238-47 and in Gogly *et al.* (2007) *Arterioscler. Thromb. Vasc. Biol*. 27:1984-90. Preferably, gingival fibroblasts are sampled and cultured in a serum-free medium in presence of platelet lysate as described in Doucet *et al.* (2005) *J Cell Physiol*. 205:228-36. In particular, gingival fibroblasts can be obtained by culturing a gingival sample or biopsy, optionally after enzymatic digestion of the sample or the biopsy to free gingival fibroblasts therefrom. As such, the cells originating from the culture of a gingival sample or biopsy are essentially gingival fibroblasts.

The gingival fibroblast extract can be obtained by any cell fragmentation method known in the art. Preferably the gingival fibroblast extract according to the

invention is selected from the group consisting of a membrane extract, a cytoplasmic extract or a nuclear extract.

Preferably, the gingival fibroblast conditioned medium according to the invention relates to a liquid cell-culture medium, in particular a serum-free culture medium and/or a culture medium comprising platelet lysate, which has been contacted by gingival fibroblasts, in particular for a time sufficient for the gingival fibroblasts to have secreted in the medium. Thus, the gingival fibroblast conditioned medium according to the invention contains gingival fibroblast secretions.

It is well within the common skills of one of ordinary skill in the art to determine which culture medium is suitable for gingival fibroblast in it. In particular, the culture can be of any type known to one of ordinary skill in the art to sustain survival and/or growth of gingival fibroblasts. By way of example of suitable gingival fibroblast conditioned medium according to the invention stand Dulbecco's Modified Eagle's Medium (DMEM), Eagle's Minimum Essential Medium (MEM or EMEM), Eagle's Minimum Essential Medium Alpha Modification (Alpha MEM) and Basal Medium Eagle (BME).

Preferably, the gingival fibroblasts have been in contact with the culture medium for at least 2, 4, 6, 8, 10, 12, 24, 36 or 48 hours. Preferably also, the gingival fibroblasts have been in contact with the culture medium for less than 72, 56 or 48 hours.

The gingival fibroblast conditioned medium according to the invention can be subjected to treatment steps such as centrifugation, filtration, or concentration. In particular, the gingival fibroblast conditioned medium according to the invention can be a concentrated gingival fibroblast conditioned medium, more particularly a gingival fibroblast conditioned medium concentrated 2, 5, 10, 25 or 50 times with respect to the unconcentrated gingival fibroblast conditioned medium from which it derives.

Preferably, the gingival fibroblast-derived product for use according to the invention comprises:

- taking the gingival fibroblasts from the individual;
- culturing the gingival fibroblasts;
- obtaining a gingival fibroblast-derived product from the cultured gingival fibroblasts;
- administering the gingival fibroblast-derived product to the individual.

Preferably, gingival fibroblasts according to the invention are autologous, which means they are taken from the individual to whom the gingival fibroblast-derived product is intended to be administered. However, the gingival fibroblasts according to the invention can also be allogenic, which means they are taken from another individual of the same species, or heterologous, which means they are taken from another individual of another species.

Administration

Preferably, the gingival fibroblast-derived product according to the invention is administered in a prophylactically or therapeutically effective amount for preventing or treating an inflammatory skin disease. Preferably also, the gingival fibroblast-derived product according to the invention is administered in a cosmetically effective amount for treating skin dryness.

The administration of the gingival fibroblast-derived product or the pharmaceutical or cosmetic composition comprising the gingival fibroblast-derived product according to the invention can proceed by any method known in the art. Preferably, the administration of the gingival fibroblast-derived product or the pharmaceutical or cosmetic composition comprising the gingival fibroblast-derived product is at a site near or on the skin area to be treated. More preferably, the gingival fibroblast-derived product or the pharmaceutical or cosmetic composition comprising the gingival fibroblast-derived product is administered subcutaneously, intravenously, intramuscularly, intra-dermally or topically, near or on the skin area to be treated. Most preferably, the gingival fibroblast-derived or the pharmaceutical or cosmetic composition comprising the gingival fibroblast derived-product is administered topically.

Preferably, the skin area to be treated according to the invention refers to a site where one or more symptoms of the inflammatory skin disease according to the invention are visible or in close proximity of this site. Preferably also, the skin area to be treated according to the invention refers to a site where one or more effects of skin dryness according to the invention are visible or in close proximity of this site.

Preferably, the gingival fibroblast-derived product or the pharmaceutical or cosmetic composition comprising the gingival fibroblast-derived product is under the form of a lotions, a cream, an ointment, a gel, a sprays a wipe, a pad or a patch.

Additional compounds

The agent for the prevention or treatment of the inflammatory skin disease according to the invention, in particular atopic dermatitis, can be of any type known to one of ordinary skill in the art. Preferably, the agent for the prevention or treatment of atopic dermatitis and/or inflammatory skin rashes according to the invention is selected from the group consisting of a corticosteroid, a calcineurin inhibitor, an emollient, and a moisturizer.

The corticosteroid according to the invention can be of any type well known to one of ordinary skill in the art such as dexamethasone, betamethasone, prednisolone, prednisone, tixocortol and triamcinolone.

The calcineurin inhibitor can be of any type well known to one of ordinary skill in the art such as cyclosporine and cyclosporine modified.

The emollient according to the invention can be of any type well known to one of ordinary skill in the art such as paraffin, silicon, dimethicon, arachydyl alcohol, cetyl stearyl, cearyl alcohol, palm glycerides, mineral oil, petrolatum, oleic acid, ethyl linoleate, glyceride derivatives, lanoline and glycerol.

The moisturizer according to the invention can be of any type well known to one of ordinary skill in the art such as a cream, an ointment and a lotion.

Pharmaceutical composition

As intended herein, "pharmaceutically acceptable carrier or excipient" refers to any material suitable with a pharmaceutical composition. Preferably, the pharmaceutically acceptable carrier or excipient according to the invention is suitable for a topical administration.

Preferably, the pharmaceutically acceptable carrier or excipient according to the invention, includes but is not limited to any of the standard carrier or excipient known to one of ordinary skill in the art such as water, glycerine, alcohol, oil emulsion, water emulsion, buffered saline solution, preservative, stabilizer and wetting agents.

Non-therapeutic use

As intended herein, "skin dryness" according to the invention refers to a non-pathological dry skin. Skin dryness according to the invention is preferably associated with a red patch, a dry patch, visible dry lines, a discoloration of the skin, scabs, superficial burns, a feeling of skin tightness a skin irritation.

The cosmetic agent intended for the cosmetic treatment of skin dryness according to the invention can be of any type known to one of ordinary skill in the art. The cosmetic agent intended for the cosmetic treatment of skin dryness according to the invention is preferably selected from the group consisting of a moisturizer, an emollient, a hypoallergenic emollient, an ointment, soap-free products, a dermatological gel and a dermatological bar.

As intended herein, "cosmetically acceptable carrier or excipient" refers to any material which is suitable with a cosmetic composition. Preferably, the cosmetically acceptable carrier or excipient is suitable for a topical administration.

The cosmetically acceptable carrier or excipient according to the invention include but is not limited to any of the standard cosmetic carrier or excipient known to one of ordinary skill in the art such as water, vegetal oil, mineral oil, fatty acid alcohol and natural waxes.

The invention will be further described by the following non-limiting figures and Example.

Description of the figures

Figure 1A and 1B

Figures 1A and 1B represent the level of secretion (vertical axis pg/ml) of CCL26 (Figure 1A) and TSLP (Figure 1B) by keratinocytes in a simultaneous treatment. The experiment was conducted in low inflammatory condition. Dexamethasone (black bars) has been tested at 10µM, 100 µM and 500 µM compared to the control (hatched bar).

Figure 2

Figure 2 represents the level of secretion (vertical axis pg/ml) of CCL26 by keratinocytes in a simultaneous treatment. The experiment was conducted in low inflammatory condition. Two batches of conditioned medium from various gingival fibroblasts donors have been used GF009 (dotted bar) and GF010 (hatched bar) compared to the control (grey bar). The two batches of conditioned medium have been tested at the concentration 5X.

Figures 3A, 3B, and 3C

Figures 3A, 3B and 3C represent the level of secretion (vertical axis pg/ml) of CCL26 (Figure 3A), TSLP (Figure 3B) and IL-1β (Figure 3C) by keratinocytes in a simultaneous treatment. The experiment was conducted in high inflammatory condition. Two batches of conditioned media from various gingival fibroblasts donors have been used GF009 (dotted bar) and GF010 (hatched bar) compared to the control (grey bar). The two batches of conditioned media have been tested at the concentration 5X.

Figures 4A, and 4B

Figures 4A and 4B represent the level of secretion (vertical axis pg/ml) of CCL26 by keratinocytes in a deferred treatment. The experiment was conducted in low inflammatory condition. Two batches of conditioned media from various gingival fibroblasts donors have been used GF009 (dotted bar) and GF015 (hatched bar) compared to the control (grey bar). The two batches of conditioned media have been tested in two different concentrations: 5X and 50X and collected on day 2 (Figure 4A) and day 5 (Figure 4B).

Example

A. Material and methods

1. Human gingival fibroblasts

1.1. Culture cell

Human gingival fibroblasts (GF) were obtained from healthy donors. After enzymatic dissociation of gingival biopsies (collagenase, dispase), gingival fibroblasts were cultured in a serum-free medium in presence of platelet lysate (Doucet et *al.* (2005) *J Cell Physiol*. 205:228-36).

1.2. Preparation of gingival fibroblast conditioned medium

The culture medium of confluent GF was discarded. After rinsing (PBS), fresh medium was added (without platelet lysate and without antibiotics). Cells were incubated at 37°C for 24 hours. The conditioned medium (CM) was collected, aliquoted and stored at -80°C. These steps can be performed with different passage cells.

1.3 Concentration of CM

The media were centrifuged on a concentration membrane (Millipore, Amicon 3K) and then stored at -80°C.

2. Human keratinocytes

Keratinocytes were obtained from breast reconstruction of healthy donors. For expansion, cells were seeded into irradiated feeders in a suitable medium.

3. Protocol

3.1. Induction of inflammation

A same combination of pro-inflammatory agents (IL-4, IL-13, TNFa, polyinosinic:polycytidylic acid (polyI:C) was used at 2 different concentrations:

- Low concentration: IL-4 10ng/ml, IL-13 10ng/ml, TNFa 5ng/ml, polyI:C 5µg/ml;
- High concentration: IL-4 100ng/ml, IL-13 100ng/ml, TNFa 20ng/ml, polyI:C 10µg/ml.

3.2. Anti-inflammatory treatment

3.2.1. Reference products

Dexamethasone (from 100 µM to 500µM) (Sigma Aldrich)

3.2.2. Gingival fibroblast conditioned medium

The gingival fibroblast conditioned medium was concentrated for use at a final concentration from 5X to 50X. Three batches of conditioned media from various gingival fibroblasts donors have been used (GF009, GF010 and GF015)

3.3. Optimising the time of treatment

For the efficacy tests of CM, keratinocytes were seeded without feeder in 6-well plates with a medium suitable for cell culture without feeder (KSFM medium, Gibco).

4. Test procedure

4.1. Simultaneous treatment for the induction of inflammation

When the keratinocyte culture reached confluence, the culture medium of keratinocytes was replaced by a medium containing the pro-inflammatory agents (day 0) and the anti-inflammatory treatment (reference product or gingival fibroblast conditioned medium). The medium was collected on day 1 and stored at -80°C until analysis.

4.2. Deferred treatment for the induction of inflammation

When the keratinocyte culture reached confluence, the culture medium of keratinocytes was replaced by a medium containing pro-inflammatory agents (day 0). On day 1, the gingival fibroblast conditioned medium was directly added in the medium containing pro-inflammatory cytokines. The medium was collected on day 2 or day 5 and stored at -80°C until analysis.

4.3. Analysis

The inflammatory condition of keratinocytes was determined by measuring inflammatory cytokine levels in their culture media. The studied cytokines were CCL26, TSLP and IL-1β. These cytokines were quantified with an ELISA assay (Duoset kit, R&D system).

B. Results

The present Example is based on an *in vitro* model of atopic dermatitis comprising:

(i) growing keratinocytes until they reach confluence,

(ii) stimulating them using a cocktail of pro-inflammatory agents, including PolyI:C, tumour necrosis factor (TNF-a), IL-4 and IL-13, known to be involved in atopic dermatitis inducement (Castex-Rizzi *et al.* (2014) *British Journal of Dermatology* 170(suppl. S1):12-18; Le *et al.* (2009) *Allergy* 64:1226-1235) and

(iii) determining the level of inflammatory cytokines/chemokines (TSLP, CCL26 and IL-1β) known to be involved in the pathogenesis of atopic dermatitis (Castex-Rizzi *et al. op. cit.*, Le *et al. op. cit.*, Cianferoni *et al. op. cit.* Kagami *et al. op. cit.* Sera *et al. op. cit.*) in the presence or absence of gingival fibroblast (GF) conditioned medium.

1. Anti-inflammatory effect of reference products (simultaneous treatment)

Results presented in **Figures 1A-1B** show that dexamethasone inhibits the secretion of CCL26 (**Figure1A**) and TSLP (**Figure 1B**).

This model is thus relevant and dexamethasone can serve as reference product to evaluate the efficacy of gingival fibroblast conditioned medium to inhibit secretion of pro-inflammatory cytokines.

2. Anti-inflammatory effect of the gingival fibroblast conditioned medium (simultaneous treatment)

2.1. Induction of inflammation with a low concentration of inflammatory agents

Results presented in **Figure 2** show that the two tested batches of gingival fibroblast conditioned medium (GF009 and GF010) inhibit the secretion of CCL26 by inflammatory keratinocytes at the concentration 5X. Similar results were obtained for the secretion of TSLP and IL-1β.

2.2. Induction of inflammation with a high concentration of inflammatory agents

Figures 3A-3C show that gingival fibroblast conditioned medium inhibits the secretion of CCL26 (**Figure 3A**), TSLP (**Figure 3B**) and IL-1β (**Figure 3C**)

2.3. Conclusion

Gingival fibroblast conditioned medium has an inhibitory effect on the secretion of inflammatory cytokines CCL26, TSLP and IL-1β by keratinocytes exposed to inflammatory conditions, even under highly inflammatory conditions.

3. Anti-inflammatory effect of the gingival fibroblast conditioned medium (deferred treatment)

3.1. Induction of inflammation

The two tested batches of gingival fibroblast conditioned medium (GF009 and GF010) inhibit the secretion of inflammatory cytokine CCL26 by inflammatory keratinocytes either at the concentrations 5X or 50X when collected on day 2 (**Figure 4A**) and on day 5 (**Figure 4B**).

3.2. Conclusion

Gingival fibroblast conditioned medium has a long term inhibitory effect on the secretion of inflammatory cytokines by keratinocytes exposed to inflammatory conditions, even when the inflammatory conditions are established for 24 hours before the keratinocytes are treated by the conditioned medium.

CLAIMS

1. A gingival fibroblast-derived product for use in the treatment or prevention of an immune-related disease in an individual.

2. The gingival fibroblast-derived product for use according to claim 1, wherein the immune-related disease is selected from the group consisting of an inflammatory disease, an auto-immune disease and an allergic disease.

3. The gingival fibroblast-derived product for use according to claim 1 or 2, wherein the immune-related disease is selected from the group consisting of inflammatory skin disease, asthma and arthritis.

4. The gingival fibroblast-derived product for use according to any of claims 1 to 3, wherein the immune-related disease is atopic dermatitis.

5. The gingival fibroblast-derived product for use according to any of claims 1 to 4, wherein the gingival fibroblast-derived product is selected from the group consisting of gingival fibroblast whole cells, a gingival fibroblast culture, a gingival fibroblast extract and a gingival fibroblast conditioned medium.

6. The gingival fibroblast-derived product for use according to any of claims 1 to 5, wherein the gingival fibroblast-derived product is obtained from gingival fibroblasts taken from the individual.

7. The gingival fibroblast-derived product for use according to any of claims 1 to 6, comprising:

- taking gingival fibroblasts from the individual;
- culturing the gingival fibroblasts;
- obtaining a gingival fibroblast-derived product from the cultured gingival fibroblasts;
- administering the gingival fibroblast-derived product to the individual.

8. The gingival fibroblast-derived product for use according to any of claims 1 to 7, wherein the gingival fibroblast-derived product is associated with at least one agent intended for the prevention or treatment of inflammatory skin disease.

9. The gingival fibroblast-derived product for use according to any of claims 1 to 8, wherein the gingival fibroblast-derived product is associated with at least one agent intended for the prevention or treatment of inflammatory skin disease selected from the group consisting of a corticosteroid, a calcineurin inhibitor, an emollient, a moisturizer.

10. The gingival fibroblast-derived product according to any of claims 1 to 9, wherein the gingival fibroblast-derived product is administered topically.

11. A composition comprising a gingival fibroblast-derived product as defined in any of claims 1 and 5 to 7, further comprising at least one agent intended for the prevention or treatment of inflammatory skin disease as defined in claim 8 or 9, and optionally comprising at least one pharmaceutically acceptable carrier or excipient.

12. The composition according to claim 11, for use in the treatment or prevention of an immune related disease as defined in any of claims 2 to 4.

13. The non-therapeutic use of a gingival fibroblast-derived product for the cosmetic treatment of skin dryness of an individual.

14. The non-therapeutic use according to claim 13, wherein the gingival fibroblast-derived product is associated with a least one cosmetic agent intended for the cosmetic treatment of skin dryness.

15. The non-therapeutic use according to claim 13 or 14, wherein the cosmetic agent intended for the cosmetic treatment of skin dryness is selected from the group consisting of a moisturizer, an emollient, and an ointment.

16. A cosmetic composition comprising a gingival fibroblast-derived product and at least one cosmetic agent intended for the cosmetic treatment of skin dryness, and optionally at least one cosmetically acceptable carrier or excipient.

17. The cosmetic composition according to claim 16, wherein the cosmetic agent intended for the cosmetic treatment of skin dryness is selected from the group consisting of a moisturizer, an emollient, and an ointment.

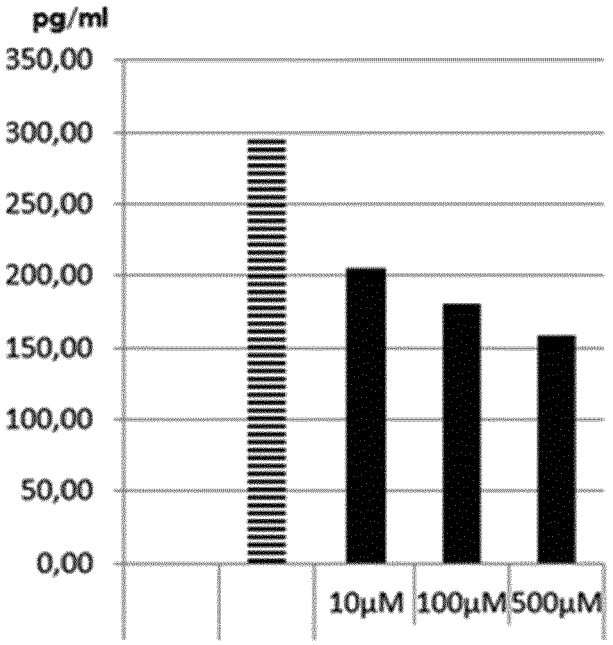

Figure 1A

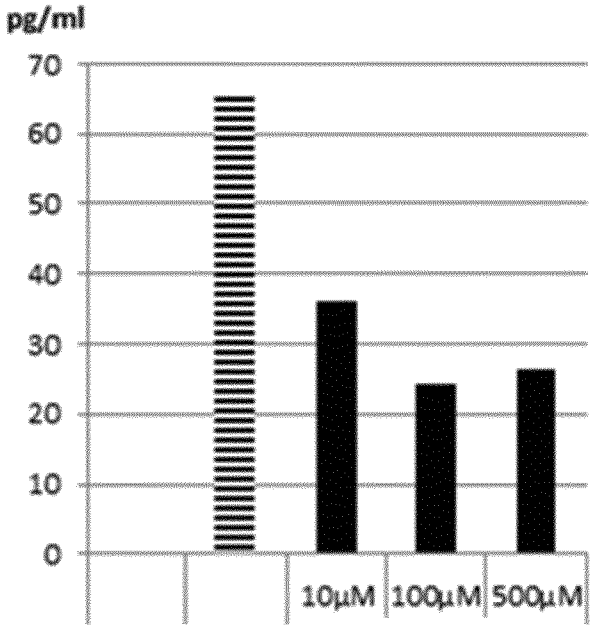

Figure 1B

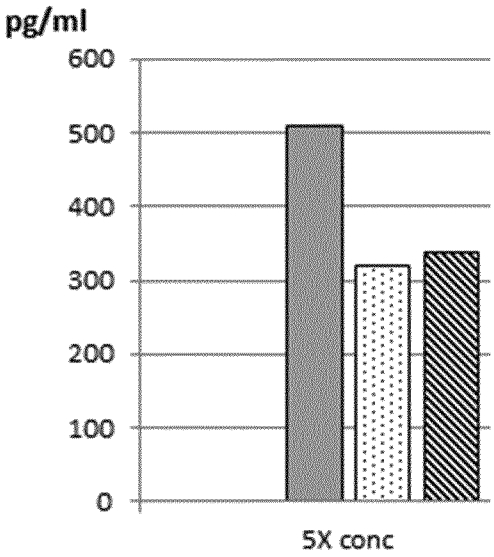

Figure 2

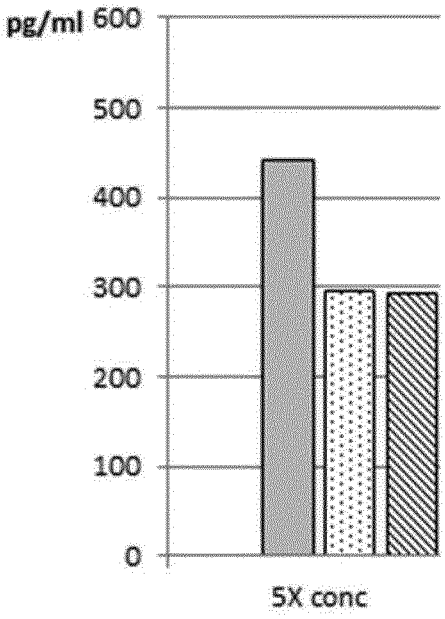

Figure 3A

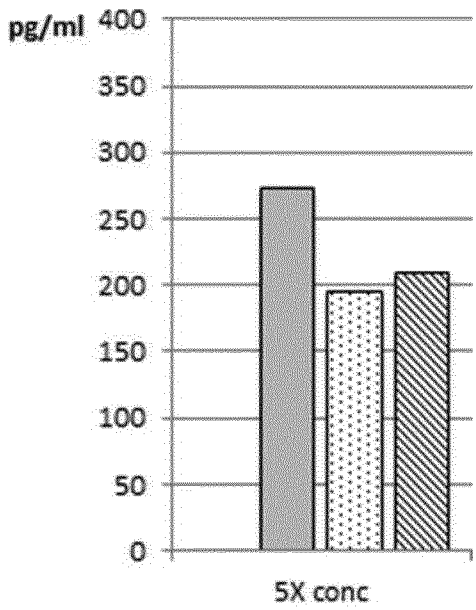

Figure 3B

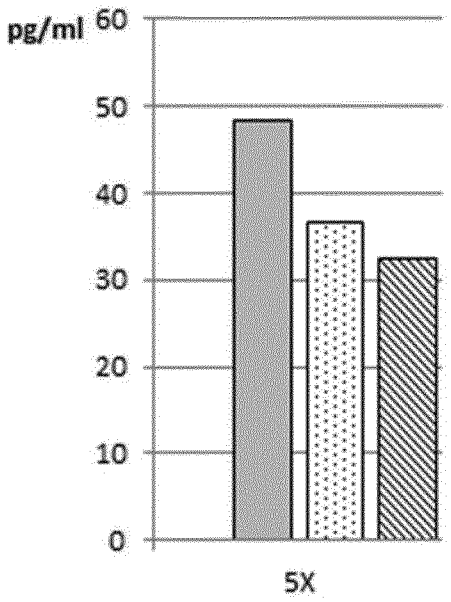

Figure 3C

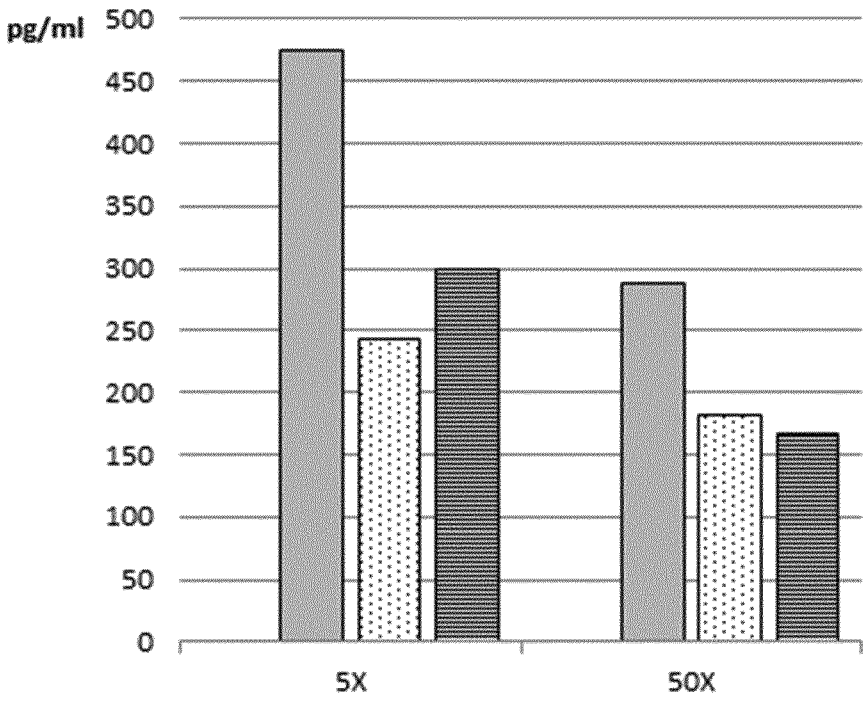

Figure 4A

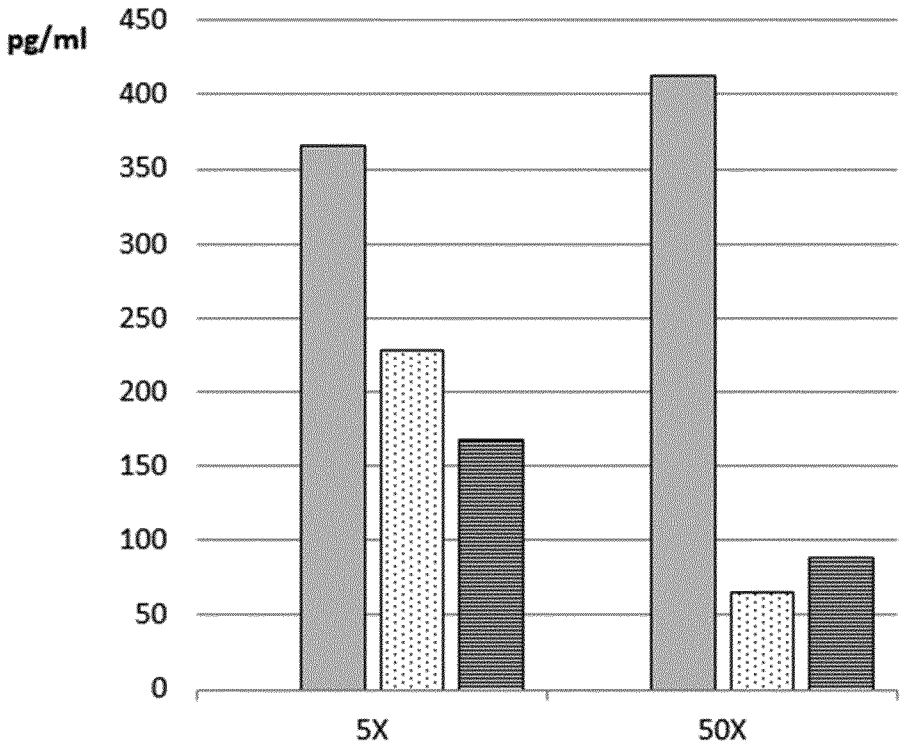

Figure 4B

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/079698

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K35/36 A61Q19/00 A61K8/98 A61P37/00 A61P17/06
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 A61Q A61P

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, WPI Data, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	page 1, line 1 - page 2, line 12 page 4, line 11 - line 21 page 7, line 14 - page 8, line 37 figure 4 claims	1-17

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2018	28/03/2018

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, Fax: (+31-70) 340-3016	Greif, Gabriela

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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