

METHODS OF TREATING SKIN DISORDERS

FIELD

[0001] Described herein are methods for treating or alleviating symptoms associated with a skin disorder such as acne vulgaris, using pharmaceutical compositions and agents which inhibit or reduce the expression one or more genes such as CXCL13, SPP1, MMP12 and MMP13.

BACKGROUND

[0002] The following discussion is provided to aid the reader in understanding the disclosure and is not admitted to describe or constitute prior art thereto.

[0003] Acne vulgaris (AV) is one of the most common skin disorder, and it has a multifactorial, complex pathogenesis that centers on pilosebaceous units. In acne-prone skin, inflammatory processes may precede the development of a visibly apparent lesion in skin that appears otherwise clinically normal. Thus, targeting inflammation is an essential part of acne therapy.

[0004] Compounds with activity of retinoid type (vitamin A and its derivatives) are widely known for their potential in the treatment or prevention of dermatologic conditions, including acne. Several of the biological effects of retinoids are mediated by modulating the nuclear retinoic acid receptors (RAR), which activate transcription by binding to DNA sequence elements, known as RAR response elements (RARE), in the form of a heterodimer with the retinoid X receptors (known as RXRs). Three subtypes of human RARs have been identified and described: RAR α , RAR β and RAR γ . Conventional topical retinoids have differing receptor binding profiles to retinoic acid receptor (RAR) subtypes, which may translate to clinical differences and likely affect suites of genes that could result in class effects (such as normalization of epithelial turnover) as well as specific functional responses to an individual retinoid, particularly in activation or suppression of inflammatory pathways.

[0005] There remains a need to develop novel therapeutic regimes to treat patients with skin disorders, particularly those suffering from acne, including acne vulgaris taking in to consideration the genetic processes and regulatory mechanisms at the molecular level and how variations in gene expression and receptor binding may translate to differences in the clinical treatment.

SUMMARY

[0006] Provided herein are methods for treating a skin disorder in a subject and pharmaceutical compositions for use in the treatment of a skin disorder, such as acne vulgaris.

[0007] In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition that inhibits CXCL13 activity.

[0008] In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition that inhibits MMP12 and/or MMP13 activity.

[0009] In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition exhibiting combined CXCL13 inhibitory activity and MMP12 and/or MMP13 inhibitory activity.

[0010] In one or more embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a pharmaceutical agent and a pharmaceutically acceptable carrier. In one or more embodiments, the pharmaceutical agent inhibits the activity of or reduces the expression of one or more genes selected from CXCL13, MMP12 and MMP13.

[0011] In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject in need thereof, the method comprising administering to a subject

in need thereof, a pharmaceutical composition, wherein said pharmaceutical composition reduces the expression of one or more genes selected from CXCL13, MMP12 and MMP13.

[0012] In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition that reduces the expression of CXCL13.

[0013] In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition that reduces the expression of MMP12 and/or MMP13.

[0014] In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition that reduces the expression of combined CXCL13 and MMP12 and/or MMP13.

[0015] In one or more embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a pharmaceutical agent and a pharmaceutically acceptable carrier. In one or more embodiments, the pharmaceutical agent reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13.

[0016] In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject in need thereof, the method comprising administering to a subject in need thereof, a pharmaceutical composition, wherein said pharmaceutical composition reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13.

[0017] In one or more embodiments, the pharmaceutical composition comprises from about 1 µg/g to about 100 µg/g of a pharmaceutical agent. In one or more embodiments, the pharmaceutical agent is administered once daily, twice daily, once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks. In one or more embodiments, the

pharmaceutical composition is formulated as a cream or as an oil-in-water emulsion. In one or more embodiments, the pharmaceutical composition is formulated as a cream.

[0018] In one or more embodiments, the subject has acne. In one or more embodiments of the methods, the skin disorder is acne vulgaris. In one or more embodiments of the methods, the skin disorder is acne vulgaris of the face or trunk. In one or more embodiments of the methods, the acne vulgaris comprises mild, moderate and severe acne vulgaris. In one or more embodiments, the pharmaceutical composition is administered topically to the area of the subject affected with acne vulgaris.

[0019] In one or more embodiments, there are provided methods of modulating an adaptive immune response in a subject to effect a treatment of a skin disorder, comprising administering to the subject a pharmaceutical composition that inhibits the activity of or reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13.

[0020] In one or more embodiments, there are provided methods of alleviating inflammatory response associated with skin disorders in a subject, comprising administering to the subject a pharmaceutical composition that inhibits the activity of or reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13. In one or more embodiments, the skin disorder is acne vulgaris and the method comprises treating acne vulgaris. In one or more embodiments, the method decreases inflammation in the skin of the subject.

[0021] In one or more embodiments, there are provided methods of antagonizing CXCR5 receptor activity in a patient suffering from acne vulgaris, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical agent which inhibits the activity of or reduces the expression of CXCL13.

[0022] In one or more embodiments, there are provided methods of monitoring or determining efficacy of an acne treatment in a subject, the method comprising determining in a sample from said subject the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13. In one or more embodiments, the subject is treated with a pharmaceutical composition

that inhibits the activity of or reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13. In one or more embodiments of the method, a decrease or an increase in the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13 in the sample relative to the controls is used to determine the efficacy of the acne treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 illustrates methodology for biopsy sampling in acne patients.

[0024] FIG. 2 illustrates a Venn diagram comparing the number of candidates for differentially expression genes following the analyses of trifarotene treatment vs spontaneously resolved papule signature (NPS-R3 vs NPS-L1), the papule signature (NPS-L1 vs NPS-LNI), and the signature of a papule after vehicular treatment (NPS-L3 vs NPS-L1).

[0025] FIG. 3 illustrates genes which are uniquely downregulated by trifarotene and involved in inflammatory cell infiltration and extracellular matrix reorganization

[0026] FIG. 4 illustrates the ingenuity pathway analysis of trifarotene specific gene signature.

[0027] FIG. 5 (A) and 5 (B) illustrates open target analyses of trifarotene and papule signature showing the diseases and pathways regulated by trifarotene specific genes.

DETAILED DESCRIPTION

[0028] Embodiments according to the present disclosure will be described more fully hereinafter. Aspects of the disclosure may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. The terminology used in the description herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[0029] Unless otherwise defined, all terms (including technical and scientific terms) used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. It will be further understood that terms, such as those defined in commonly used dictionaries, should be interpreted as having a meaning that is consistent with their meaning in the context of the present application and relevant art and should not be interpreted in an idealized or overly formal sense unless expressly so defined herein. While not explicitly defined below, such terms should be interpreted according to their common meaning.

[0030] The terminology used in the description herein is for the purpose of describing particular embodiments only and is not intended to be limiting of the invention. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety.

[0031] Unless the context indicates otherwise, it is specifically intended that the various features of the invention described herein can be used in any combination. Moreover, the disclosure also contemplates that in one or more embodiments, any feature or combination of features set forth herein can be excluded or omitted. To illustrate, if the specification states that a complex comprises components A, B and C, it is specifically intended that any of A, B or C, or a combination thereof, can be omitted and disclaimed singularly or in any combination.

[0032] Unless explicitly indicated otherwise, all specified embodiments, features, and terms intend to include both the recited embodiment, feature, or term and biological equivalents thereof.

Definitions

[0033] As used herein, the singular forms “a,” “an,” and “the” designate both the singular and the plural, unless expressly stated to designate the singular only.

[0034] It is to be understood, although not always explicitly stated, that all numerical designations are preceded by the term “about.” The term “about” means that the number

comprehended is not limited to the exact number set forth herein, and is intended to refer to numbers substantially around the recited number while not departing from the scope of the invention. As used herein, “about” will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, “about” will mean up to plus or minus 15%, 10%, 5%, 1%, or 0.1% of the particular term.

[0035] Also as used herein, “and/or” refers to and encompasses any and all possible combinations of one or more of the associated listed items, as well as the lack of combinations when interpreted in the alternative (“or”). Thus, acne vulgaris includes acne vulgaris of the face, acne vulgaris of the trunk, or acne vulgaris of the face and trunk.

[0036] The terms “administer,” “administration,” or “administering” as used herein refer to (1) providing, giving, dosing and/or prescribing, such as by either a health professional or his or her authorized agent or under his direction, and (2) putting into, applying, taking or consuming, such as by a health professional or the subject. For example, administration can include without limitation, topical routes of administration (e.g., gel, ointment, cream, aerosol, etc.) and can be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, excipients, and vehicles appropriate for each route of administration. The invention is not limited by the route of administration, the formulation or dosing schedule.

[0037] The terms “treat”, “treating” or “treatment”, as used herein, include alleviating, attenuating, abating or ameliorating skin disorders, or one or more symptoms thereof, whether or not the skin disorder is considered to be “cured” or “healed” and whether or not all symptoms are resolved. The terms also include reducing or preventing progression of a skin disorder or one or more symptoms thereof, impeding or preventing an underlying mechanism of the skin disorder or one or more symptoms thereof, and achieving any therapeutic and/or prophylactic benefit.

[0038] As used herein, the term “subject” is used interchangeably with “patient,” and indicates a mammal, in particular a human, equine, bovine, porcine, feline, canine, murine, rat, or non-human primate. In one or more embodiments, the subject is a human.

[0039] As used herein, the term “equivalent thereof” as used herein, include, for example, salts, precursors, derivatives, esters, polymorphs, etc. of the therapeutic active agent. For example, an equivalent of trifarotene can include pharmaceutically acceptable salts thereof.

[0040] The term “precursors” means the immediate biological precursors or substrates thereof, and also the chemical precursors thereof.

[0041] The term “derivatives” means both the metabolic derivatives thereof and the chemical derivatives thereof.

[0042] An “effective amount” is an amount sufficient to effect beneficial or desired results such as alleviating at least one or more symptom of a skin condition or disorder, such as for example, acne vulgaris. An effective amount as used herein would also include an amount sufficient to delay the development of or alter the course of the skin disorder and/or a symptom (for example low self-esteem), or reverse a symptom of the skin disorder. Thus, it is not possible to specify the exact “effective amount.” However, for any given case, an appropriate “effective amount” can be determined by one of ordinary skill in the art using only routine experimentation. For example, the effective amount of pharmaceutical agent or composition may include the use of a thin layer of a topical composition sufficient to cover the area to be treated.

[0043] In one or more embodiments, the skin disorder such as acne vulgaris are scored as clear, almost clear, mild, moderate, or severe. “clear,” “almost clear,” “mild,” “moderate,” and “severe” are terms of art in describing the presence, extent, anatomical location, extent on the body, type of morphological lesions (*e.g.*, papules, pustules, nodules, cysts, scars, comedones, etc.), severity, and/or intensity of the acne. Those of skill in the art know the metes and bounds of these terms.

[0044] The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic agent is administered.

[0045] Inflammatory skin disorders are well-known and may include acne, psoriasis, hives, eczema, rosacea, vitiligo, keratosis and dermatitis. Acne vulgaris is a common chronic inflammatory skin disease with a complex pathogenesis developing in the sebaceous follicles. Four key pathogenic factors have been identified: (i) an alteration in the pattern of keratinisation within the follicle, (ii) increased sebum production, (iii) colonization with *Propionibacterium acnes*, and (iv) inflammation. In acne-prone skin, inflammatory processes may precede the development of a visibly apparent lesion in skin that appears otherwise clinically normal; thus, targeting inflammation is an essential part of acne therapy. Topical retinoids interact with nuclear receptors to affect gene transcription; specifically, their actions are mediated by retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Retinoic acid (RA) or a synthetic RAR agonist, (e.g., trifarotene) binds to RAR/RXR, enabling the formation of a co-activator complex and subsequent changes in the expression of downstream genes. The anti-inflammatory effects of topical retinoids have been well established, particularly in regards to the innate immune response. The present technology provides methods by which reducing the expression of certain genes, exhibits a direct effect on the adaptive immune system and helps attenuate the inflammatory response in skin disorders such as acne.

0046] The following abbreviations are used herein: LS = Lesional Skin, L1 = LS Before Treatment, L3 = LS After Vehicle Treatment, R3 = LS After CD5789 Treatment, L-NI = Non Involved Skin, PS = Prone Scare, and NPS = Non Prone Scare.

Therapeutic Active Agent

[0047] The therapeutic active agent or pharmaceutical agent to be used according to the technology include compounds which reduce the expression of one or more genes associated with reversal of inflammatory pathways or matrix reorganization. Examples of such genes include, but are not limited to chemokine (C-X-C motif) ligands such as *e.g.*, CXCL13, secreted

phosphoproteins such as *e.g.*, SPP1, and members of the matrix-metalloproteinase family such as *e.g.*, MMP12 and MMP13. Other examples of suitable genes are summarized in Table 1.

Suitable compounds which can reduce the expression of more genes associated with reversal of inflammatory pathways or matrix reorganization, which optionally have inhibitory activity against such genes and which can be used in the treatment of acne include, for example, retinoids, including compounds which are retinoid acid or a synthetic retinoic acid receptor (RAR) agonists. One such example of a retinoid acid receptor γ (RAR γ) agonist is trifarotene, which is a terphenyl acid derivative having the chemical name 3''-tert-Butyl-4'-(2-hydroxyethoxy)-4''-pyrrolidin-1-yl-[1,1',3',1'']terphenyl-4-carboxylic acid. Trifarotene is marketed under the trademark AKLIEF[®] at a concentration of 50 micrograms per gram (mcg/g or μ g/g), in the form of a cream.

[0048] The present inventors unexpectedly discovered that in addition to promoting epidermal differentiation and keratinization processes, retinoid acid receptors uniquely downregulate genes involved in inflammatory cell infiltration (*e.g.*, CXCL13, XCL1) and extracellular matrix reorganization (*e.g.*, SPP1/Osteopontin, MMP12, MMP13). It was also discovered that the LXR/RXR signalling is downregulated. These heretofore-unknown activities were evaluated using trifarotene as an exemplary pharmaceutical agent and acne vulgaris as an exemplary skin condition.

[0049] Subjects with moderate inflammatory acne of the back were treated with a 0.005% trifarotene or vehicle cream on dedicated back areas for 27 days, and 4 biopsies were collected on each subject (non-involved skin, acne papule, Trifarotene and vehicle treated site). Large scale gene expression profiling of the biopsies was performed using Affymetrix technology, and treatment specific gene expression profiles were generated using statistical modeling.

(I) Transcriptome data and relevance of bioinformatic analysis

[0050] To gain an enhanced understanding of how trifarotene exerts its effects in acne, a post-hoc bioinformatics analysis was performed on transcriptomics data collected from lesional and

non-lesional skin of patients with acne vulgaris with the goal of identifying genes or pathways, using the action of trifarotene as an example. The study is pioneering and compares gene expression in normal skin, spontaneously resolving acne lesions, and topical-retinoid-treated acne lesions. Bioinformatic analyses are performed to extract useful information from large amounts of raw data. Biologic and genetic data stored in sequence databases can be organized and queried. This allows study of how normal cellular activities change in individual disease states.

(II) Clinical open-label study

[0051] Clinical investigations were conducted in accordance with the Declaration of Helsinki principles, and the ICH Guideline for Good Clinical Practice. The clinical study received approval from the ethics committee of Brest, France (reference CPP Quest 6-755). This was a post-hoc analysis of data collected from 9 patients aged 18-35 with acne vulgaris. Each patient had four biopsies performed, 1 from skin without visible acne lesion and three at the site of acne papule, with the following timing: one prior to treatment (day 0), one after vehicle treatment (day 27), and one after trifarotene treatment (day 27). Aubert *et al*, *Br J Dermatol.*, 2018 Aug; 179(2):442-456.

[0052] Samples were collected for large-scale gene expression profiling. Subjects provided written informed consent prior to biopsies. Subjects with moderate inflammatory acne on the back at the screening visit, defined by scores of between 2 and 4 for the whole back, with at least one area scored at 2 and a maximum of three nodules using the ECLA (Acne Lesion Score Scale) scale, were included in the study. Each subject had at least 2 papules 48 hours old, one on each half of the back. Study personnel applied treatment to patients' backs with trifarotene cream (right side) or vehicle (left side) once daily for 28 days excluding weekends (n=19 applications). Biopsies of nonlesional areas of trifarotene- and vehicle-treated skin were made under local anaesthesia at day 27 as shown in **Fig. 1**. Biopsies were stored in RNAlater TissueProtect Tubes (Qiagen, Les Ulis, France).

[0053] Data analysis was performed using Array Studio software (Omicsoft Corporation, Cary, NC, USA). Affymetrix U133 Plus 2.0 chips (GeneChip™, Santa Clara, CA, USA) were normalized using the multi-array average (RMA) method (*See e.g.*, Irizarry RA, et al. Exploration, normalization, and summaries of high density oligonucleotide array probe level data. *Biostatistics*, 2003; 4:249-64.) Low expression probe-sets were filtered. Only Affymetrix identifiers with expression $\geq 2^6$ in at least 5 samples in one condition were selected for further statistical analysis, resulting in data for 36245 out of the 54675 probe-sets present on the HG U133 Plus 2.0 array. Mean expression levels were obtained by calculating the geometric means of the RMA-normalized data. A linear model was fitted to the normalized data, and statistical testing of the comparisons of interest were performed using a moderated t-test. Paired-test was used when applicable. P values were adjusted for multiple testing using the Benjamini-Hochberg false discovery rate (FDR) method (*See e.g.*, Benjamini Y, et al., Controlling the false discovery rate in behavior genetics research. *Behav Brain Res*, 2001;125:279-84). Candidate differentially expressed genes were selected using a combination of fold-change and FDA; genes with absolute fold change >2 and FDA <0.05 were considered as candidate differentially expressed genes.

(III) Analysis

[0054] Functional and network analysis were generated with the Ingenuity Pathway Analysis software (QIAGEN Inc., <https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis>), and with Open Targets (<https://www.opentargets.org/>).

(IV) Results

[0055] A comparative analysis was performed to identify expression patterns: For this analysis, the following comparisons were made to develop characteristic expression patterns: (a) Papule before treatment vs non-involved skin was used to derive an acne signature; (b) Resolved papule zone after treated with vehicle vs papule before treatment was used to derive signature of spontaneously resolved papule; and (c) Resolved papule zone after treatment with trifarotene vs papule before treatment to determine trifarotene treatment signature.

[0056] A summary of the analysis results is provided in **Fig. 2**, which illustrates a Venn diagram highlighting the number of candidate differentially expressed genes. A heat map highlighting gene expression changes between non-involved skin, acne lesion before/after trifarotene treatment, for 67 genes found differentially expressed in the papule signature, but also in the trifarotene signature. Gene were clustered using average linkage and correlation distance. Gene expression levels were scaled by gene (green = lower gene expression, red= higher gene expression). No clustering of the sample was performed. Color bars at the top display the clinical group of each sample: L-NI=non-involved skin, L1=papule at baseline, R3= papule after treatment with trifarotene. Results obtained using Ingenuity Pathway Analysis on the 67 genes is highlighted in **Fig. 3**. Opposite changes in gene expression were observed for pathways related to inflammatory response, leukocyte migration, neutrophil movement, and T cell migration when comparing the papule signature to the trifarotene signature (**Fig. 4**). A listing of the signature genes is provided in **Table 1** below:

Table 1

Gene Symbol	Gene Name
CXCL13	C-X-C motif chemokine ligand 13
MMP12	matrix metalloproteinase
SPP1	secreted phosphoprotein 1
ADAMDEC1	ADAM like decysin 1
MMP13	matrix metalloproteinase 13
CCNA1	cyclin A1
ADAM12	ADAM metalloproteinase domain 12
ITGAX	integrin subunit alpha X
BCAT1	branched chain amino acid transaminase 1
HP	Haptoglobin
CBLN2	cerebellin 2 precursor
CTLA4	cytotoxic T-lymphocyte associated protein 4
KLHL6	kelch like family member 6

CD80	CD80 molecule
SLAMF7	SLAM family member 7
SIRPB1	signal regulatory protein beta 1
SELP	selectin P
NCEH1	neutral cholesterol ester hydrolase 1
GLIS3	GLIS family zinc finger 3
DMXL2	Dmx like 2
GLIPR2	GLI pathogenesis related 2
EVI2B	ecotropic viral integration site 2B
NRP2	neuropilin 2
MMP19	matrix metalloproteinase 19
FERMT3	fermitin family member 3
SNAP25	synaptosome associated protein 25
IRF8	interferon regulatory factor 8
CYTH4	cytohesin 4
PAPSS2	3'-phosphoadenosine 5'-phosphosulfate synthase 2
P2RY8	P2Y receptor family member 8
HLA-DPA1	major histocompatibility complex, class II, DP alpha 1
MSR1	macrophage scavenger receptor 1
IL2RG	interleukin 2 receptor subunit gamma
LOXL2	lysyl oxidase like 2
PARVG	parvin gamma
P2RY10	P2Y receptor family member 10
GPRIN3	GPRIN family member 3
RAC2	Rac family small GTPase 2
CD37	CD37 molecule
PTH1H	parathyroid hormone like hormone
INA	internexin neuronal intermediate filament protein alpha

CD84	CD84 molecule
PTPRO	protein tyrosine phosphatase receptor type O
FNDC3B	fibronectin type III domain containing 3B
GLIPR1	GLI pathogenesis related 1
BIRC3	baculoviral IAP repeat containing 3
XCL1	X-C motif chemokine ligand 1
SLC6A14	solute carrier family 6 member 14
LY86	lymphocyte antigen 86
ARHGAP9	Rho GTPase activating protein 9
IL18BP	interleukin 18 binding protein
CLEC4A	C-type lectin domain family 4 member A
CD69	CD69 molecule
SH2B3	SH2B adaptor protein 3
TYROBP	TYRO protein tyrosine kinase binding protein
GASK1B	golgi associated kinase 1B
TRG-AS1	T cell receptor gamma locus antisense RNA 1
RHOH	ras homolog family member H
APEL	Aapelin receptor early endogenous ligand
LPXN	leupaxin
VCAN	versican
CCDC71L	coiled-coil domain containing 71 like
PTPN22	protein tyrosine phosphatase non-receptor type 22
SELPLG	selectin P ligand
LINC01224	-
PXMP4	peroxisomal membrane protein 4
GABRA4	gamma-aminobutyric acid type A receptor alpha4 subunit

[0057] Core analysis of the acne signature indicated that cellular movement and immune cell trafficking are increased in acne lesions. Pathway analyses showed positive z-scores for TREM1 signaling, crosstalk between dendritic and natural killer cells, leukocyte extravasation signaling, dendritic cell maturation, neuroinflammatory pathways, and pattern recognition receptors involved in recognition of bacteria and viruses. A negative z-score was identified for LXR/RXR activation, suggesting retinoid X receptor pathways may be inhibited in acne papules.

[0058] IPA analyses of the trifarotene signature showed a positive z-score for LXR/RXR pathways, indicating a re-activation during treatment. In addition, cellular movement and immune cell trafficking are reduced. Comparison of the profiles generated from an acne lesion with a trifarotene-treated lesion indicated there were 354 genes in common. Notably, all 354 genes were activated or deactivated in a reverse fashion in acne signature compared to trifarotene signature. Analysis of pathways and processes showed reversal of neuroinflammatory pathways, inhibition of matrix metalloproteinase, engagement of LXR/RXR pathway, and inhibition of immune migration. Trifarotene uniquely downregulated 67 genes involved in inflammatory cell infiltration (CXCL13, XCL1) and extracellular matrix reorganization (SPP1/Osteopontin, MMP12, MMP13), as shown in Fig. 3.

[0059] Core analysis of spontaneously resolving papules indicated that they include changes in pathways and processes that are similar to those seen with trifarotene therapy. It was observed that 287 genes have changes in expression across acne signature, trifarotene signature, and spontaneously resolved signature and those that are upregulated in acne are downregulated in both trifarotene and spontaneously resolving signatures. Further 69 genes were observed to overlap between acne and spontaneously resolved signatures. However, 67 genes are uniquely affected and pathway analyses of these genes demonstrated that the treatment with trifarotene is associated with reversal of inflammatory pathways and inhibition of matrix metalloproteinases. Moreover, the treatment also impacted immune cell migration including neutrophil infiltration and T cell migration as shown.

[0060] Acne lesions exhibit increased expression of genes associated with inflammation and cell infiltration. There also appears to be a downregulation of LXR/RXR signalling. The treatment appears to reverse these processes, as a total of 354 genes upregulated in acne are reversed by retinoic acid receptor compounds. Sixty-seven genes involved in inflammatory cell infiltration (CXCL13, XCL1) and extracellular matrix reorganization (SPP1/Osteopontin, MMP12, MMP13) are uniquely downregulated. Two independent systems biology approaches are used here to better characterize this list of 67 genes: Ingenuity Pathway Analysis and Open Targets. Results of the open target analyses are depicted in **FIG. 5A** and **5B**. In the Ingenuity analysis, the most significant processes identified were inflammatory response, leukocyte migration, Neutrophil cell movement and T cell migration and neutrophil infiltration, suggesting that trifarotene may reverse some inflammatory processes of the papule. The Open Targets results illustrate that acne and immune system diseases were among top processes regulated by trifarotene specific genes. Extracellular matrix remodeling is the most represented target pathway through the modulation of 8 genes: MMP12, MMP13, MMP19, ADAM12, ADAMDEC1, SSP1 and VCAM. Two targets were imputed to chemokine signaling: C- X-C motif chemokine ligand 13 (CXCL13) and X-C motif chemokine ligand (XCL1). Thus, trifarotene has a unique action in acne treatment by acting both on epidermal and immune components of acne pathogenesis.

[0061] In particular, a notable gene strongly down regulated was chemokine (C-X-C motif) ligand 13 (CXCL13), a major chemoattractant of B cells and a regulator of humoral immune responses. CXCL13 is a small chemokine belonging to the CXC chemokine family and is selectively chemotactic for B cells belonging to both the B-1 and B-2 subsets, and elicits its effects by interacting with chemokine receptor type 5 (CXCR5). CXCL13 and its receptor CXCR5 control the organization of B cells within follicles of lymphoid tissues. In T lymphocytes, CXCL13 expression is thought to reflect a germinal center origin of the T cell, particularly a subset of T cells called follicular helper T cells (or TFH cells). This suggests that trifarotene may have an effect on the adaptive immune response in the perilesional skin of acne patients. Other major genes which have reduced expression or are specifically inhibited include secreted phosphoproteins, such as SPP1, that bind to various types of calcium-based biominerals,

and members of the matrix-metalloproteinase family, such as MMP12 and MMP13, that play a role in the extra-cellular matrix reorganization and tissue remodeling, processes which may actively be involved in acne. Other examples of genes which may have reduced expression are listed in Table 1. Comparison of skin post resolution shows that the treatment also promotes epidermal differentiation and keratinization processes. Altogether, these results show that retinoic acid (RA) or a synthetic RAR agonist, such as trifarotene has a unique action in acne treatment by acting on epidermal and immune components of acne pathogenesis.

[0062] The present technology highlights a specific gene expression profile, comprised of 67 genes uniquely driven by trifarotene treatment with most of these genes known to affect immune responses as well as extracellular matrix reorganization. Interestingly, those genes were modulated in an opposite direction as compared to the untreated papule signature suggesting reversal of some inflammatory processes within the papule.

Methods

[0063] In accordance with one aspect, provided are method for treatment of a skin disorder in a subject in need thereof, the method comprising, consisting of, or consisting essentially of administering to the subject, a pharmaceutical composition, wherein said pharmaceutical composition reduces the expression of one or more genes associated with reversal of inflammatory pathways or matrix reorganization. Examples of such genes include, but are not limited to CXCL13, SPP1, MMP12 and MMP13. In accordance with one, provided are methods of treating a skin disorder in a subject, the method comprising, consisting of, or consisting essentially of administering a pharmaceutical composition that reduces the expression of CXCL13. In accordance with a second aspect, provided are methods of treating a skin disorder in a subject, the method comprising, consisting of, or consisting essentially of administering a pharmaceutical composition that reduces the expression of MMP12 and/or MMP13. In accordance with a third aspect, provided are methods of treating a skin disorder in a subject, the method comprising, consisting of, or consisting essentially of administering a pharmaceutical composition that reduces the expression of a combination of CXCL13 and MMP12 and/or

MMP13. In accordance with a fourth aspect, provided are methods of treating a skin disorder in a subject, the method comprising, consisting of, or consisting essentially of administering a pharmaceutical composition, wherein said pharmaceutical composition reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13.

[0064] In accordance with another aspect, provided are method for treatment of a skin disorder in a subject in need thereof, the method comprising, consisting of, or consisting essentially of administering to the subject, a pharmaceutical composition, wherein said pharmaceutical composition inhibits the expression or activity of one or more genes associated with reversal of inflammatory pathways or matrix reorganization. In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition that inhibits CXCL13 expression. In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition that inhibits MMP12 and/or MMP13 expression. In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject, the method comprising administering to said subject a pharmaceutical composition exhibiting combined inhibition of CXCL13 and MMP12 and/or MMP13 expression. In one or more embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a pharmaceutical agent and a pharmaceutically acceptable carrier. In one or more embodiments, the pharmaceutical agent reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13. In accordance with one or more embodiments, there are provided methods for treatment of a skin disorder in a subject in need thereof, the method comprising administering to a subject in need thereof, a pharmaceutical composition, wherein said pharmaceutical composition reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13.

[0065] The skin disorders may include dermatological conditions such as inflammatory skin disorders, skin cancers, disorders of increased cell turnover (e.g. psoriasis), photoaging, and skin

wrinkles. In one or more embodiments, the skin disorder may include, but is not limited to, acne, psoriasis, ichthyos, ichthyosiform states and palmoplantar hyperkeratosis. In one or more embodiments, the skin disorder is acne. In one or more embodiments, the skin disorder is acne vulgaris. In one or more embodiments, the skin disorder is acne vulgaris of the face and/or trunk.

[0066] The success rate of the treatment disclosed herein may be based on the IGA and PGA outcome (percentage of subjects “clear” and “almost clear” and with at least a 2-grade change from baseline) and/or the absolute and percentage change from baseline lesion counts on the face and/or trunk. The lesion counts consider the two major types of acne lesions: non-inflammatory and inflammatory. Non-inflammatory lesions of acne are the open (blackheads) or closed (whiteheads) comedones. Inflammatory lesions are divided into papules, pustules, and nodules/nodulocystic lesions, depending on the severity and location of the inflammation within the dermis. Both the absolute and percentage reduction in total number of inflammatory and/or non-inflammatory lesions on the face and/or trunk from the first day of treatment (baseline) to the end of the treatment may be used to assess the success rate. In one or more embodiments, the treatment may include reduction in inflammatory and/or noninflammatory lesion counts of the subject.

[0067] In particular embodiments, the subject has at least 20 inflammatory lesions and 25 non-inflammatory lesion counts on the face at screening and baseline. In particular embodiments, the subject has at least 20 inflammatory lesions and 20 non-inflammatory lesions but no more than 100 non-inflammatory lesion counts on the trunk (shoulders, upper back and chest, anterior chest) at screening and baseline. In one or more embodiments, the treatment may include about $\geq 10\%$ reduction in inflammatory and/or non-inflammatory lesion count on the face and/or trunk in a subject, including, but not limited to, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40% or greater than about 50% reduction in inflammatory and/or non-inflammatory lesion count.

[0068] In one or more embodiment, the treatment may include from about 5% to about 99% reduction in inflammatory and/or non-inflammatory lesion count in a subject, including, but not limited to, about 10% to about 90%, about 15% to about 85%, about 20% to about 80%, about 25% to about 75%, about 30% to about 70%, about 35% to about 65%, about 40% to about 60%, about 45% to about 50% reduction in inflammatory and/or non-inflammatory lesion count on the face and/or trunk, or any range including and/or in-between any two of these values. In one or more embodiments, the treatment includes about 20% to about 60% reduction in inflammatory and/or non-inflammatory lesion count on the face and/or trunk after 12 weeks of treatment. In one or more embodiments, the treatment includes about 30% to about 50% reduction in inflammatory and/or non-inflammatory lesion count on the face and/or trunk after 12 weeks of treatment.

[0069] The pharmaceutical composition may include a pharmaceutical agent and a pharmaceutically acceptable carrier. Suitable pharmaceutical agent includes compounds which reduce the expression of one or more genes associated with reversal of inflammatory pathways or matrix reorganization. In some embodiments, pharmaceutical agent includes compounds which reduce the expression or inhibit the expression or activity of one or more genes associated with reversal of inflammatory pathways or matrix reorganization. In one or more embodiments, the pharmaceutical agent is one that reduces the expression of chemokine (C-X-C motif) ligands such as *e.g.*, CXCL13. In one or more embodiments, the pharmaceutical agent is that reduces the expression of the secreted phosphoprotein genes such as *e.g.*, SPP1. In one or more embodiments, the pharmaceutical agent is that reduces the expression of genes from the metalloproteinase family such as *e.g.*, MMP12 and MMP13. In some embodiments, pharmaceutical agent includes compounds which inhibit the expression or activity of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13. Suitable pharmaceutical agents which reduce the expression of these genes, optionally which have such inhibitory activity and which can be used in the treatment of acne include, for example, retinoids, including compounds which are retinoid acid or a synthetic retinoic acid receptor (RAR) agonists. In one or more embodiments, the pharmaceutical agent is retinoic acid or a synthetic RAR agonist. In one or

more embodiments, the pharmaceutical agent includes trifarotene or an equivalent thereof. In one or more embodiments, the pharmaceutical agent does not include trifarotene or a pharmaceutically acceptable salt thereof. In one or more embodiments, the pharmaceutical agent is not trifarotene. In one or more embodiments, the pharmaceutical agent is retinoic acid or a synthetic RAR agonist other than trifarotene.

[0070] An effective amount can be administered in one or more administrations, applications or dosages. Such delivery is dependent on a number of variables including the time period for which the individual dosage unit is to be used, the bioavailability of the therapeutic agent, the route of administration, etc. The pharmaceutical compositions or formulations may be delivered to the subject by various routes of administration, *e.g.*, by topical administration, transdermal administration, oral administration, by nasal administration, rectal administration, subcutaneous injection, intravenous injection, intramuscular injection, or intraperitoneal injection. It is understood, however, that specific dose levels of the therapeutic agents of the present disclosure for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the drug combination, skin absorption for topical compositions, systemic absorption in general for topical and oral compositions, and the severity of the particular disorder being treated and form of administration. Treatment dosages generally may be titrated to optimize safety and efficacy. The dosage can be determined by a physician and adjusted, as necessary, to suit observed treatment effects and to manage and adapt to retinoid dermatitis.

[0071] In one or more embodiments, creams, ointments, foams or lotions which includes from about 1 µg/g to about 100 µg/g of the pharmaceutical agent is topically administered to the subject, including, but not limited to, from about 5 µg/g to about 95 µg/g, about 10 µg/g to about 90 µg/g, about 15 µg/g to about 85 µg/g, about 20 µg/g to about 80 µg/g, about 25 µg/g to about 75 µg/g, about 30 µg/g to about 70 µg/g, about 35 µg/g to about 65 µg/g, about 40 µg/g to about 60 µg/g, about 45 µg/g to about 55 µg/g, about 46 µg/g to about 54 µg/g, about 47 µg/g to about

53 µg/g, about 48 µg/g to about 52 µg/g, or about 49 µg/g to about 51 µg/g. In certain embodiments, a cream which includes from about 1 µg/g to about 100 µg/g of the pharmaceutical is topically administered to the subject. In certain embodiments, a cream which includes about 50 µg/g of the pharmaceutical agent is topically administered once daily to the affected area of the subject.

[0072] In one or more embodiments, the effective amount of the pharmaceutical agent ranges from about 0.0001 weight percent to about 0.1 weight percent, about 0.001 weight percent to about 0.5 weight percent, about 0.005 weight percent to about 1 weight percent, about 0.01 weight percent to about 1.5 weight percent, or about 0.1 weight percent to about 10 weight percent. In particular embodiments, the effective amount of the pharmaceutical agent is about 0.0001 weight percent, about 0.005 weight percent, about 0.1 weight percent, about 1 weight percent, about 2 weight percent, or about 2.5 weight percent, or any range including and/or in-between any two of these values, and/or as needed based on the appearance of symptoms of the skin disorder. In particular embodiments, the effective amount of the pharmaceutical agent is a 2 g flat dose (*e.g.* in cream form). In one or more embodiments, the pharmaceutical agent is administered by a topical route. In one or more embodiments, the pharmaceutical agent is administered by applying a thin layer enough to cover the area being treated.

[0073] In one or more embodiments, the pharmaceutical composition described herein is administered thrice daily, twice daily, once daily, every other day, twice per week, three times per week, four times per week, five times per week, six times per week, once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every nine weeks, once every 10 weeks, once every 11 weeks, once every 12 weeks, twice per year, once per year, or any range including and/or in-between any two of these values, and/or as needed based on the appearance of symptoms of the skin disorder. In one or more embodiments, the pharmaceutical composition is administered once daily.

[0074] The treatments have a variable duration, depending on the patient and the severity of the facial and/or acne. The treatment period may thus run from several days to several years. In one or more embodiments, the duration of treatment is about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, about 29 days, about 30 days, about one week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 10 weeks, about 20 weeks, about 30 weeks,, about 36 weeks, about 40 weeks, about 48 weeks, about 50 weeks, about one year, about two years, about three years, about four years, about five years, or any range including and/or in-between any two of these values, and/or as needed based on the appearance of symptoms of the skin disorder. In one or more embodiments, duration of treatment is about 10 days to about 35 days, about 25 days to about 30 days, about 12 to about 48 weeks, or about 24 to about 36 weeks.

[0075] In accordance with another aspect, provided are methods of modulating an adaptive immune response in a subject to effect a treatment of a skin disorder, comprising administering to the subject a therapeutically effective amount of a trifarotene or an equivalent thereof and a pharmaceutically acceptable carrier. In one or more embodiments, the skin disorder is acne vulgaris. In one or more embodiments, the skin disorder is acne vulgaris of the face and/or trunk, including moderate acne vulgaris of the face and trunk.

[0076] In accordance with one aspect, provided are methods of preventing, attenuating, alleviating or treating inflammatory response associated with skin disorders in a subject, comprising topically administering to the subject a therapeutically effective amount of a pharmaceutical agent and a pharmaceutically acceptable carrier. Suitable pharmaceutical agents are described herein and include compounds which inhibit the activity of or reduce the expression of one or more genes associated with reversal of inflammatory pathways or matrix reorganization such as *e.g.*, CXCL13, SPP1, MMP12 and MMP13. In one or more

embodiments, the skin disorder is acne vulgaris and the method comprises treating acne vulgaris. In one or more embodiments, the method decreases inflammation in the skin of the subject.

[0077] In accordance with another aspect, provided are methods of antagonizing CXCR5 receptor activity in a patient suffering from acne vulgaris, consisting of administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical agent which inhibits the activity of or reduces the expression of one or more genes associated with reversal of inflammatory pathways such as *e.g.*, CXCL13.

[0078] In accordance with another aspect, provided are methods monitoring or determining efficacy of a skin disorder treatment, including an acne treatment in a subject, the method comprising determining in a sample from said subject the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13. In one or more embodiments, the acne is acne vulgaris. In one or more embodiments, the subject is treated with a pharmaceutical composition, which includes trifarotene or an equivalent thereof. In one or more embodiments, a decrease or an increase in the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13 in the sample relative to the controls is used to determine the efficacy of the acne treatment. The present technology also provides methods for diagnosing or detecting inflammatory response in a subject suffering from a skin disorder, *e.g.*, acne vulgaris, comprising determining in a sample from said subject, a decrease or an increase in the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13 in the sample relative to the controls is used to determine the efficacy of the acne treatment. The controls can be subjects who have not undergone the treatment with the pharmaceutical agent.

Pharmaceutical Compositions

[0079] Provided herein are pharmaceutical compositions for use in the methods described herein, the composition comprising, consisting of, or consisting essentially of a pharmaceutical agent. In one or more embodiments, the pharmaceutical agent is a retinoid, or an equivalent thereof. In one or more embodiments, the pharmaceutical agent is a retinoid, such as trifarotene

or an equivalent thereof. In one or more embodiments, the pharmaceutical agent includes trifarotene or a pharmaceutically acceptable salt thereof. In one or more embodiments, the pharmaceutical composition may include a therapeutically effective amount trifarotene or an equivalent thereof and a pharmaceutically acceptable carrier. In one aspect, the present technology provides a pharmaceutical composition for alleviating inflammation associated with skin disorders comprising trifarotene or an equivalent thereof and a pharmaceutically acceptable carrier.

[0080] In one aspect, the present technology provides a pharmaceutical composition including a pharmaceutical agent and a pharmaceutically acceptable carrier. One of ordinary skill in the art will appreciate that the term "effective amount" may not require successful treatment be achieved in a particular individual. In some embodiments, effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. In some embodiments, an effective amount may be formulated and/or administered in a single dose. In other embodiments, an effective amount may be formulated and/or administered in a plurality of doses, for example, as part of a dosing regimen. In one or more embodiments, the effective amount may be an effective amount for treating a skin disorder (*e.g.*, acne vulgaris), for modulating an adaptive immune response, for preventing, attenuating, alleviating or treating inflammatory response associated with skin disorders, for antagonizing CXCR5 receptor activity, for monitoring or determining efficacy of an acne treatment or for diagnosing or detecting inflammatory response in a subject.

[0081] It is recognized that pharmaceutical compositions may be provided in the form of a cream or a foam which may be dispensed from a tube or a pump. In some embodiments, the pharmaceutical compositions may be packed as a 50 mL bottle with pump and over cap. In some embodiments, the pharmaceutical composition provided herein includes an effective amount of an active ingredient, which includes an amount (and/or a concentration) sufficient so that a single actuation of a pump containing the composition produces an effective amount. In some embodiments, more than one actuation of the pump may be required to produce an effective

amount of active ingredient. For example, one pump actuation may include an amount of the pharmaceutical composition which is enough to cover the face (*i.e.*, forehead, cheeks, nose, and chin), two actuations of the pump may include an amount of the pharmaceutical composition which is enough to cover the upper trunk (*i.e.*, reachable upper back, shoulders and chest). In some embodiments, one additional pump actuation may be used for application to the middle and lower back if acne is present.

[0082] The pharmaceutical compositions described herein may contain various carriers or excipients known to those skilled in the art. Such excipients and carriers are described, for example, in “Remington’s Pharmaceutical Sciences” Mack Pub. Co., New Jersey (1991), which is incorporated herein by reference. Suitable carriers or excipients may include, but are not limited to, emollients, ointment base, emulsifying agents, solubilizing agents, humectants, thickening or gelling agents, wetting agents, texture enhancers, stabilizers, pH regulators, osmotic pressure modifiers, emulsifiers, UV-A and UV-B screening agents, preservatives, permeation enhancer, chelating agents, antioxidants, acidifying agents, alkalizing agents, buffering agents and vehicle or solvent. In one or more embodiments, the pharmaceutically acceptable carrier includes a liquid, paste or solid form, and more particularly in the form of ointments, creams, milks, pomades, powders, impregnated pads, syndets, solutions, gels, sprays, foams, pastes, suspensions, sticks, shampoos or washing bases. It may also be in the form of suspensions of microspheres or nanospheres or of lipid or polymer vesicles or gelled or polymer patches allowing a controlled release.

[0083] The pharmaceutical compositions of any embodiment herein may be formulated for topical administration or any of the routes discussed herein. In one or more embodiments, pharmaceutical compositions may be formulated as a composition for topical administration. The pharmaceutical compositions of the present technology are particularly suited for topical treatment of the skin, and may be in the form of ointments, creams, milks, pomades, powders, impregnated pads, solutions, gels, gel-creams, sprays, lotions, foams or suspensions.

[0084] All publications, patents, and patent applications cited in this specification are incorporated herein by reference in their entireties as if each individual publication, patent or patent application were specifically and individually indicated to be incorporated by reference. While the foregoing has been described in terms of various embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions, and changes may be made without departing from the spirit thereof.

CLAIMS

1. Use of a pharmaceutical composition, wherein said pharmaceutical composition reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13, in the manufacture of a medicament for the treatment of a skin disorder in a subject in need thereof, and wherein the said medicament is to be administered.
2. Use of a pharmaceutical composition that reduces the expression of CXCL13, in the manufacture of a medicament for the treatment of a skin disorder in a subject, wherein said medicament is to be administered.
3. Use of a pharmaceutical composition that reduces the expression of MMP12 and/or MMP13, in the manufacture of a medicament for the treatment of a skin disorder in a subject, wherein said medicament is to be administered.
4. Use of a pharmaceutical composition that reduces the expression of SPP1, in the manufacture of a medicament for the treatment of a skin disorder in a subject, wherein said medicament is to be administered.
5. The use according to any of the preceding claims, wherein the pharmaceutical composition comprises a therapeutically effective amount of a pharmaceutical agent and a pharmaceutically acceptable carrier.
6. The use according to any of the preceding claims, wherein the pharmaceutical composition comprises from about 1 µg/g to about 100 µg/g of a pharmaceutical agent.
7. The use according to according to claim 5 or claim 6, wherein the pharmaceutical composition is administered once daily, twice daily, once per week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, or once every eight weeks.
8. The use according to any of the preceding claims, wherein the pharmaceutical composition is formulated as a cream or as an oil-in-water emulsion.

9. The use according to any of the preceding claims, wherein the skin disorder is acne vulgaris.
10. The use according to any of the preceding claims, wherein the skin disorder is acne vulgaris of the face or trunk.
11. The use according to any of the preceding claims, wherein the acne vulgaris comprises mild, moderate and severe acne vulgaris.
12. The use according to any of the preceding claims, wherein the pharmaceutical composition is to be topically administered to the area of the subject affected with acne vulgaris.
13. Use of a pharmaceutical composition that reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13, in the manufacture of a medicament for modulating an adaptive immune response in a subject to effect a treatment of a skin disorder, wherein said medicament is to be administered.
14. Use of a pharmaceutical composition that reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13, in the manufacture of a medicament for alleviating inflammatory response associated with skin disorders in a subject, wherein said medicament is to be administered.
15. The use of claim 14, wherein the skin disorder is acne vulgaris and the method comprises treating acne vulgaris.
16. The use of claim 14, wherein the method decreases inflammation in the skin of the subject.
17. Use of a therapeutically effective amount of a pharmaceutical agent which reduces the expression of CXCL13, in the manufacture of a medicament for antagonizing CXCR5 receptor activity in a patient suffering from acne vulgaris, wherein said medicament is to be administered.

18. A method of monitoring or determining efficacy of an acne treatment in a subject, the method comprising determining in a sample from said subject the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13.

19. The method of claim 18, wherein the subject prior to the monitoring, has already been treated with a pharmaceutical composition that reduces the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13.

20. The method of claim 18, wherein a decrease or an increase in the expression of one or more genes selected from CXCL13, SPP1, MMP12 and MMP13 in the sample relative to the controls is used to determine the efficacy of the acne treatment.