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(54) Title: COMPOSITIONS COMPRISING BACTERIOPHAGES AND USES THEREOF FOR THE TREATMENT OR PREVENTION OF SKIN LESIONS AND PSORIASIS

(57) Abstract: Provided herein is phage therapy for the treatment and control of psoriasis, skin lesions and infections. More particularly, provided is a composition comprising bacteriophage and uses thereof. Provided herein is a method of making the composition comprising one or more strains of bacteriophage. Also provided is a method of treating and preventing a skin disorder such as psoriasis or skin lesions. Also provided herein is a dermatological composition comprising one or more strains of bacteriophage and cosmetic use thereof.

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COMPOSITIONS COMPRISING BACTERIOPHAGES AND USES THEREOF FOR THE TREATMENT OR PREVENTION OF SKIN LESIONS AND PSORIASIS

1. INTRODUCTION

[0001] The present disclosure relates to phage therapy for the treatment and control of psoriasis, skin lesions and infections. More particularly, the present disclosure relates to a composition comprising bacteriophage and uses thereof. Provided herein is a method of making the composition comprising one or more strains of bacteriophage. Also provided is a method of treating and preventing a skin disorder such as psoriasis or skin lesions. Also provided herein is a dermatological composition comprising one or more strains of bacteriophage and cosmetic use thereof.

2. BACKROUND

[0002] Psoriasis is a multifaceted immune-mediated skin disease and has been associated with poorer quality of life, increased health care burden, and other comorbidities (American Academy of Dermatology Work Group et al. 2011). The number of subjects with psoriasis is estimated to be 125 to 250 million people (Armstrong 2017). Psoriasis patients have an increased risk of developing psoriatic arthritis that further reduce their quality of life (Alinagphi et al. 2018). In 2014, WHO member states recognized psoriasis as a serious disease. Recent biologics treatment developed for psoriasis has improved prognosis for some patients but the current pricing can restrict their use (Al Sawah et al. 2017). Despite advances in new therapies, psoriasis continues to have public health impact to the society (Helmick et al. 2013). Symptoms of psoriasis are not only physically debilitating, they also have psychological effects on patients (Clausen et al 2017, Randa et al. 2018). In addition, infections of psoriatic skins are usually treated by antibiotics, however antibiotic resistance can result from such treatments. This creates problem for the patients if their infections become resistance to antibiotic treatments.

[0003] However, previous research only focused on the bacteria component of skin microbiota, other components of skin microbiota such as the bacteriophage (phage) has been neglected. The present disclosure goes beyond the conventional bacteria-focused microbiome research and unravels the less known phage components of skin microbiota in psoriasis. As

DNA shotgun sequencing technique and analysis tools advances, a higher resolution and novel interrogation of environmental DNA samples becomes practical. This enables researchers to begin to uncover new discoveries for the less studied phage component of skin microbiota.

[0004] There is a need for bacteriophage-based probiotic with or without bacteria-based probiotics. There is also a need for a composition comprising bacteriophages for phage-based therapies to treat psoriasis, skin lesions and infections. The therapy is useful for suppressing unhealthy bacteria on psoriatic skins which then lead to healthier skin. In addition, there is also a need for phage-based treatments for infections which reduces the risk of antimicrobial resistance.

3. SUMMARY

[0005] The present disclosure provides bacteriophage therapy that enables the restoration of the equilibrium of the microbiome in treated lesion areas. The present disclosure also discloses a skin care product for cosmetic use that restore and maintain the condition of healthy skin in a subject.

[0006] Provided herein is a composition comprising one or more bacteriophage strains selected from the group consisting of Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Bacillus phage SP-10, Pseudomonas phage O4, Haemophilus phage Aaphi23, Enterobacteria phage SfI, Bordetella virus BPP1, Mycobacterium phage DrDrey, Burkholderia virus BcepC6B, Rhodoferax phage P26218, Burkholderia virus phi1026b, Idiomarinaceae phage Phi1M2-2，Ralstonia phage RSK1, Sulfitobacter phage NYA-2014a, Thalassomonas phage BA3, Pseudomonas phage KPP25, Pseudomonas phage NP1, and Pseudomonas virus F116 or a variant thereof, said variant having at least 80% sequence identity to NCBI accession Nos: YP_009007647.1(Acinetobacter phage Presley), YP_009009926.1(Salmonella phage vB_SenS-Ent2), YP_007003398.1(Bacillus phage SP-10), YP_009304497.1(Pseudomonas phage O4), NP_852738.1(Haemophilus phage Aaphi23), YP_009147451.1(Enterobacteria phage SfI), NP_958679.1(Bordetella virus BPP1), YP_008409492.1(Mycobacterium phage DrDrey), YP_024932.1(Burkholderia virus BcepC6B), YP_009222582.1(Rhodoferax phage P26218), NP_945032.1(Burkholderia virus phi1026b), YP_009104301.1(Idiomarinaceae phage Phi1M2-2), YP_008853829.1(Ralstonia phage RSK1), YP_009146206.1(Sulfitobacter phage NYA-2014a), YP_001552271.1(Thalassomonas phage BA3), YP_009030589.1(Pseudomonas phage

KPP25), YP_009285843.1(Pseudomonas phage NP1), and YP_164304.1(Pseudomonas virus F116), respectively.

[0007] Provided herein is a composition comprising one or more bacteriophage strains selected from the group consisting of Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Bacillus phage SP-10, Pseudomonas phage O4, Haemophilus phage Aaphi23, Enterobacteria phage SfI, Bordetella virus BPP1, Mycobacterium phage DrDrey, Burkholderia virus BcepC6B, Rhodoferax phage P26218, Burkholderia virus phi1026b, Idiomarinaceae phage Phi1M2-2，Ralstonia phage RSK1, Sulfitobacter phage NYA-2014a, Thalassomonas phage BA3, Pseudomonas phage KPP25, Pseudomonas phage NP1, and Pseudomonas virus F116, or a variant thereof, said variant having at least 80% sequence identity to NCBI accession Nos: YP_009007647.1(Acinetobacter phage Presley), YP_009009926.1(Salmonella phage vB_SenS-Ent2), YP_007003398.1(Bacillus phage SP-10), YP_009304497.1(Pseudomonas phage O4), NP_852738.1(Haemophilus phage Aaphi23), YP_009147451.1(Enterobacteria phage SfI), NP_958679.1(Bordetella virus BPP1), YP_008409492.1(Mycobacterium phage DrDrey), YP_024932.1(Burkholderia virus BcepC6B), YP_009222582.1(Rhodoferax phage P26218), NP_945032.1(Burkholderia virus phi1026b), YP_009104301.1(Idiomarinaceae phage Phi1M2-2), YP_008853829.1(Ralstonia phage RSK1), YP_009146206.1(Sulfitobacter phage NYA-2014a), YP_001552271.1(Thalassomonas phage BA3), YP_009030589.1(Pseudomonas phage KPP25), YP_009285843.1(Pseudomonas phage NP1), and YP_164304.1(Pseudomonas virus F116), respectively.

[0008] Also provided is a composition wherein the bacteriophage shows antibacterial activity against at least one of Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia or Rhodoferax.

[0009] Provided herein is a composition comprising one or more bacteriophage strains selected from Acinetobacter phage Presley, Pseudomonas phage O4, or a variant thereof, said variant having at least 50% sequence coverage and 70 % sequence identity to SEQ ID NO:01 and 02 (sequence information provided in Supplementary Appendix), respectively.

[0010] Provided herein is a composition wherein the bacteriophage shows antibacterial activity against one or more bacterial strains selected from Acinetobacter, or Pseudomonas.

[0011] Provided herein is a composition comprising one or more bacteriophage strains selected from Acinetobacter phage Presley, Pseudomonas phage O4, or a variant thereof, said

variant having at least 50% sequence coverage and 70 % sequence identity to SEQ ID NO:01 and 02 (sequence information provided in Supplementary Appendix), respectively.

[0012] Provided herein is a composition comprising bacteriophage that shows antibacterial activity against one or more strains selected from Acinetobacter or Pseudomonas.

[0013] Provided herein is a pharmaceutical composition comprising bacteriophages; and a pharmaceutically acceptable carrier.

[0014] In one embodiment, the composition is a dermatological composition.

[0015] In certain embodiments, the pharmaceutical composition further comprises an antibiotic agent and/or an agent for treating psoriasis.

[0016] Also provided herein is a method of treating or preventing psoriasis in a subject comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition.

[0017] In certain embodiments, the psoriasis is associated with an area of intact skin. In certain embodiments, the psoriasis is associated with an area of non-intact skin.

[0018] In certain embodiments, the pharmaceutical composition is administered topically to the subject. In certain embodiments, the pharmaceutical composition is administered to the subject's elbow, forearm, knee and scalp.

[0019] In certain embodiments, the pharmaceutical composition is administered to a subject at a skin area with lesion.

[0020] Provided herein is a method of cosmetic treatment comprising applying a dermatological composition on a subject.

[0021] Provided herein is a method for improving condition of a subject's skin by modifying the microbiome in the subject comprising contacting the subject's skin with a composition disclosed herein.

[0022] In certain embodiments, the dermatological composition is administered to a subject at a skin area without lesion.

[0023] In certain embodiments, the dermatological composition is administered to a subject at a skin area with lesion.

[0024] Provided herein is a method for preparing a composition comprising producing at least one bacteriophage strain selected from the group consisting of Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Bacillus phage SP-10, Pseudomonas phage O4, Haemophilus

phage Aaphi23, Enterobacteria phage SfI, Bordetella virus BPP1, Mycobacterium phage DrDrey, Burkholderia virus BcepC6B, Rhodoferax phage P26218, Burkholderia virus phi1026b, Idiomarinaceae phage Phi1M2-2， Ralstonia phage RSK1, Sulfitobacter phage NYA-2014a, Thalassomonas phage BA3, Pseudomonas phage KPP25, Pseudomonas phage NP1, and Pseudomonas virus F116, or a variant thereof, said variant having at least 80% sequence identity to NCBI accession Nos: YP_009007647.1(Acinetobacter phage Presley), YP_009009926.1(Salmonella phage vB_SenS-Ent2), YP_007003398.1(Bacillus phage SP-10), YP_009304497.1(Pseudomonas phage O4), NP_852738.1(Haemophilus phage Aaphi23), YP_009147451.1(Enterobacteria phage SfI), NP_958679.1(Bordetella virus BPP1), YP_008409492.1(Mycobacterium phage DrDrey), YP_024932.1(Burkholderia virus BcepC6B), YP_009222582.1(Rhodoferax phage P26218), NP_945032.1(Burkholderia virus phi1026b), YP_009104301.1(Idiomarinaceae phage Phi1M2-2), YP_008853829.1(Ralstonia phage RSK1), YP_009146206.1(Sulfitobacter phage NYA-2014a), YP_001552271.1(Thalassomonas phage BA3), YP_009030589.1(Pseudomonas phage KPP25), YP_009285843.1(Pseudomonas phage NP1), and YP_164304.1(Pseudomonas virus F116), respectively, and combining the bacteriophage strains with a suitable carrier or excipient.

[0025] In certain embodiments, psoriasis and skin lesion are characterized by a microbiome of low diversity, comprising predominantly bacteria of the Pseudomonas species, Acinetobacter species, and Cutibacterium acnes species than in the microbiome of non-lesion areas and/or health controls.

[0026] Provided herein is a method for diagnosis of psoriasis comprising the steps of:

a) measuring the level of bacteria and bacteriophages in a sample from an area of a subject's skin to be tested;

b) comparing the measurement obtained from step a) to a control; and

c) determining whether the individual has a risk of developing psoriasis.

[0027] In certain embodiments, a lower level of at least one of Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Bacillus phage SP-10, Pseudomonas phage O4, Pseudomonas phage KPP25, Pseudomonas phage NP1, Pseudomonas virus F116, Haemophilus phage Aaphi23, Enterobacteria phage SfI, Bordetella virus BPP1, Mycobacterium phage DrDrey, Burkholderia virus BcepC6B, and/or Rhodoferax phage P26218 as compared to a control and/or

a higher level of Pseudomonas, Acinetobacter and/or Cutibacterum acnes as compared to a control indicates an increased risk of developing psoriasis lesions.

4. BRIEF DESCRIPTION OF THE DRAWINGS

[0028] FIG. 1 shows distribution of most abundant species in phage community and bacterial community across different samples.

[0029] FIG. 2 shows comparison of Beta Diversity PCoA1 for Phage and Bacterial Species community Between Lesional Skin and Healthy Skin.

[0030] FIG. 3 shows abundance between lesional skin and healthy skin for top ten most abundant phage species.

[0031] FIG. 4 shows comparison of different levels of phage abundance to the host bacterial abundance.

[0032] FIG. 5. Order of Top Ten Most Abundant Phage Species.

[0033] FIG. 6. Order of Top Ten Most Abundant Bacterial Species.

[0034] FIG. 7. P values of Statistical Tests for Top Ten Most Abundant Phages.

[0035] FIG. 8. Comparison of Beta Diversity PCoA1 for Phage (A) and Bacterial (B) Species Community Between Two Groups of Sex.

[0036] FIG. 9A. PCoA Plot Illustrating Differences of Phage Species Composition Between Female and Male.

[0037] FIG. 9B. PCoA Plot Illustrating Differences of Bacterial Species Composition Between Female and Male.

[0038] FIG. 10. Comparison of Alpha Diversity for Phage (A) and Bacterial (B) Species Between Lesional Skin and Healthy Skin.

[0039] FIG. 11A. PCoA Plot Illustrating Differences of Phage Species Composition Between Lesional Skin and Healthy Skin.

[0040] FIG. 11B. PCoA Plot Illustrating Differences of Bacterial Species Composition Between Lesional Skin and Healthy Skin.

[0041] FIG. 12. Order of Top Ten Most Abundant Category Two Phage Species.

[0042] FIG. 13. Differential abundance between lesional skin and healthy skin for dominate category two phage species.

[0043] FIG. 14. Suggested minimum starting % level of Potential Probiotics Phage Species.

4.1 Definitions

[0044] The term "skin" herein encompasses both the skin and the scalp, but does not comprise mucous membranes.

[0045] The term “microbiome” means all genomes of bacteria present at the surface of a skin area.

[0046] The term "lesion area" means an area of the skin affected by a disease or disorder.

[0047] The lesion areas are in particular characterized by skin dryness, redness, blisters, scabs or combinations thereof.

[0048] The terms "non-lesion area", "non-pathological area" or "healthy area" refer to an area of the skin not affected by a skin disease or disorder, and preferably not affected by any other pathology or cutaneous wound. The area of a sample generally has a surface with diameter of 0.5-2 cm. In some embodiments, the non-lesion area is a healthy area that is on the contralateral skin site to the lesion area.

[0049] The term “antibiotics” herein refers to compounds that either kill or inhibit the growth of bacteria.

[0050] The term "isolated" with respect to a bacteriophage means that the phage has been measurably increased in concentration by any purification process, including but not limited to, isolation from the environment or culture, e.g., isolation from culture following propagation and/or amplification, centrifugation, etc., thereby partially, substantially, nearly completely, or completely removing impurities, such as host cells and host cell components. For example, an isolated phage meant for use in therapeutic compositions intended for administration to humans ordinarily must be of high purity in accordance with regulatory standards and good manufacturing processes.

[0051] As used herein, the term "variant" in the context of nucleic acid sequences (e.g. from Genbank database) refers to a nucleic acid sequence that comprises or consists of a nucleic acid sequence having a sequence identity of at least 80-85%, 85-90%, 90-93%, 93-95%, 95-96%,

96-97%, 97-98%, 98-99%, 99-99.5% or more with a reference nucleic acid sequence. A variant may be selected that maintains one or more function of the reference nucleic acid sequence. For example, a variant bacteriophage may exhibit at least one biological activity, e.g., antibacterial activity (e.g., lytic killing activity), of the bacteriophage from which it is derived.

[0052] As used herein, the term "coverage" refers to the percentage of a query sequence represented in the alignment with the reference sequence.

[0053] As used herein, the term "in combination" refers to the use of an additional prophylactic and/or therapeutic agent as well as a composition comprising combination of different strains. The use of the term "in combination" does not restrict the order in which prophylactic and/or therapeutic agents are administered to a subject. A first prophylactic or therapeutic agent can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second prophylactic or therapeutic agent (different from the first prophylactic or therapeutic agent) to a subject.

[0054] As used herein, the terms "prophylactic agent" and "prophylactic agents" refer to an agent, such as a bacteriophage composition of the invention, which can be used in the prevention, management, or control of one or more symptoms of a disease or disorder, such as but not limited to, psoriasis or skin lesion.

[0055] As used herein, the terms "therapeutic agent" and "therapeutic agents" refer to an agent, such as a bacteriophage composition, that can be used in the treatment, management, or control of one or more symptoms of a disease or disorder, in particular, a disease or disorder.

[0056] As used herein, the terms "treat", "treatment" and "treating" refer to obtaining a therapeutic benefit in a subject receiving a pharmaceutical or dermatological composition. With respect to achieving a therapeutic benefit, the object is to eliminate, lessen, decrease the severity of, ameliorate, or slow the progression of the symptoms or underlying cause (e.g., bacterial infection) associated with the pathological condition or disorder. A "therapeutically effective amount" refers to that amount of a therapeutic agent, such as a pharmaceutical composition of

the invention, sufficient to achieve at least one therapeutic benefit in a subject receiving the pharmaceutical composition.

[0057] As used herein, the terms "prevent", "prevention" and "preventing" refer to obtaining a prophylactic benefit in a subject receiving a pharmaceutical or dermatological composition. With respect to achieving a prophylactic benefit, the object is to delay or prevent the symptoms or underlying cause (e.g., psoriasis, skin lesion or bacterial infection) associated with the pathological condition or disorder. A "prophylactically effective amount" refers to that amount of a prophylactic agent, such as a pharmaceutical or dermatological composition disclosed herein, sufficient to achieve at least one prophylactic benefit in a subject receiving the pharmaceutical or dermatological composition.

[0058] As used herein, the terms "antibacterial activity" and "antimicrobial activity", with reference to a bacteriophage (or variant thereof) or bacteriophage product, are used interchangeably to refer to the ability to kill and/or inhibit the growth or reproduction of a microorganism, in particular, the bacteria of the species or strain that the bacteriophage infects. In certain embodiments, antibacterial or antimicrobial activity is assessed by culturing bacteria, e.g., Gram-positive bacteria, Gram-negative bacteria or bacteria not classified as either Gram-positive or Gram-negative, according to standard techniques (e.g., in liquid culture or on agar plates), contacting the culture with a bacteriophage or variant thereof of the invention and monitoring cell growth after said contacting. For example, in a liquid culture, the bacteria may be grown to an optical density ("OD") representative of a mid-point in exponential growth of the culture; the culture is exposed to one or more concentrations of one or more bacteriophage of the invention, or variants thereof, and the OD is monitored relative to a control culture. Decreased OD relative to a control culture is representative of a bacteriophage exhibiting antibacterial activity (e.g., exhibits lytic killing activity). Similarly, bacterial colonies can be allowed to form on an agar plate, the plate exposed to one or more bacteriophage of the invention, or variants thereof, and subsequent growth of the colonies evaluated related to control plates. Decreased size of colonies, or decreased total numbers of colonies, indicate a bacteriophage with antibacterial activity.

[0059] The term “synergistic effect” refers to the interaction between two or more agents when the combined effect is larger than the sum of the effects of the individual components.

[0060] The terms "subject" and "patient" are used interchangeably herein. The terms "subject" and "subjects" refer to an animal, such as a mammal including a non-primate (e.g., a cow, pig, horse, cat, dog, rat, and mouse) and a primate (e.g., a monkey such as a cynomolgous monkey, a chimpanzee and a human)., and for example, a human.

[0061] The term "therapeutically effective amount" includes an amount of an agent or composition that, when administered to a subject for treatment, is sufficient to effect such treatment. A "therapeutically effective amount" can vary depending on, *inter alia*, the compound, the infection and its severity, and the age, weight, etc., of the subject to be treated.

[0062] The term “about” refers to $\pm$0.5 for a numerical value.

[0063] The term “resistant”, “resistance” and “develop resistance” when refer to bacteria or bacterial infections that are no longer responsive to an agent that was previously effective in reducing the bacterial growth or preventing any increase in bacterial growth.

5. DETAILED DESCRIPTION

[0064] In the following detailed description, numerous specific details are set forth to provide a thorough understanding of claimed subject matter. However, it will be understood by those skilled in the art that claimed subject matter may be practiced without these specific details. In other instances, methods, apparatuses, or systems that would be known by one of ordinary skill have not been described in detail so as not to obscure claimed subject matter. It is to be understood that particular features, structures, or characteristics described may be combined in various ways in one or more implementations.

5.1 Bacteriophage

[0065] The present disclosure is directed to phage therapy for the treatment and control of skin condition including psoriasis, skin lesion and bacterial infections. In one aspect, the invention relates to novel compositions of different bacteriophage strains. The composition may comprise at least two different isolated strains of bacteriophage, for example, two, three, four, five, six, seven, eight, nine, ten, or more different isolated bacteriophage strains. The

composition may be used alone or in further combination with other therapies, e.g., antibiotic agents or probiotic agents.

[0066] Composition comprising different strains of bacteriophage provide advantages to the use of phages individually, e.g., to increase the lytic activity against a particular bacterial strain and/or to decrease the possibility of emergence of bacteria resistant to an individual bacteriophage. Different bacteriophage can be mixed in a composition to broaden their properties, preferably resulting in a collectively greater antibacterial spectrum of activity. However, few phage composition exist with antimicrobial activity against different bacteria, probably because of the difficulty in combining different specificities of bacteriophage strains, while maintaining infecting ability and/or lytic activity of the individual bacteriophage in the presence of distinct bacteriophage strains.

[0067] In certain embodiments, the disclosure provides a composition comprising at least one isolated bacteriophage strains, including but not limited to, phage Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Bacillus phage SP-10, Pseudomonas phage O4, Haemophilus phage Aaphi23, Enterobacteria phage SfI, Bordetella virus BPP1, Mycobacterium phage DrDrey, Burkholderia virus BcepC6B, Rhodoferax phage P26218, or a combination thereof. In certain embodiments, the composition is formulated with at least two, three, four, five, six, seven, eight, nine, ten, eleven, twelve different isolated bacteriophage strains. In certain embodiments, the composition is a topical formulation. In certain embodiments, the composition is useful for the treatment and/or prevention of psoriasis and bacterial infections.

[0068] In certain embodiments, the composition comprises at least two different isolated bacteriophage strains, with antibacterial activity against the same or different bacterial strains. In certain embodiments, the therapeutic components of the composition target two or more strains of bacteria. In certain embodiments, the composition comprises 2 phage strains, 3 phage strains, 4 phage strains, 5 phage strains, 6 phage strains, 7 phage strains, 8 phage stains, 9 phage strains, 10 phage strains. In certain embodiments, the composition comprises 2-4 phage strains, 4-6 phage strains, 6-8 phage strains, 8-10 phage strains, or 10-12 phage strains. In certain embodiments, the combination does not impair or reduce (or does not substantially or significantly impair or reduce) infecting ability and/or lytic activity of the individual bacteriophage in the presence of distinct bacteriophage strains.

[0069] In certain embodiments, at least one phage strain of the composition is a strain with antibacterial activity against at least one Gram-negative bacterium, including but not limited to Acinetobacter and Pseudomonas; and/or against at least one Gram-positive bacteria including but not limited to Bacillus.

[0070] In certain embodiments, the composition comprises at least two different isolated bacteriophage strains where the strains show antibacterial activity against at least one of Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia, Rhodoferax or a combination thereof.

[0071] In some embodiments, the invention provides a composition comprising one or more strains of bacteriophage having a genome comprising or consisting of the nucleic acid sequence of SEQ ID NO:01 and 02 (sequence information provided in Supplementary Appendix), which bacteriophage exhibits at least one biological activity, e.g., antimicrobial or antibacterial activity (e.g., lytic killing activity).

[0072] In certain embodiments, provided herein is a variant bacteriophage strain which comprises or consists of a genome having a sequence identity of at least about 80-85%, 85-90%, 90-93%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more with the nucleic acid sequence as provided in NCBI accession Nos: YP_009007647.1(Acinetobacter phage Presley), YP_009304497.1(Pseudomonas phage O4), YP_009030589.1(Pseudomonas phage KPP25), YP_009285843.1(Pseudomonas phage NP1),YP_164304.1(Pseudomonas virus F116), which bacteriophage exhibits at least one biological activity, e.g., antimicrobial or antibacterial activity (e.g., lytic killing activity), of bacteriophage, Acinetobacter phage Presley, Pseudomonas phage O4, Pseudomonas phage KPP25, Pseudomonas phage NP1, and Pseudomonas virus F116.

[0073] Bacteriophage may be isolated from a bacterial sample using any method described herein or known in the art (see, e.g., Carlson, "Working with bacteriophage: common techniques and methodological approaches," In, Kutter and Sulakvelidze (Eds) Bacteriophage: Biology and Applications, 5th ed. CRC Press (2005); incorporated herein by reference in its entirety). Bacteriophage also may be isolated from any other bacterial strain susceptible to infection by one or more of the bacteriophage, and in which the bacteriophage replicate.

5.2 Combination Therapy

[0074] The composition comprising the bacteriophage as described herein may be optionally delivered with other antibacterial agents in the form of antibacterial composition, or individually, yet close enough in time to have a synergistic effect on the treatment of the psoriasis, skin lesions or infection. An antibacterial composition is a mixture of any one of the compounds described herein with another antibacterial drug. In one embodiment, a common administration vehicle (e.g., tablet, implants, injectable solution, injectable liposome solution, etc.) is used for the compound as described herein and other antibacterial agent(s). In certain embodiments, the composition comprises an antibacterial agent. In certain embodiments, the composition does not comprise an antibacterial agent. In certain embodiments, the composition is a phage-based probiotics with bacteria-based probiotics. In certain embodiments, the composition is a phage-based probiotics without bacteria-based probiotics.

5.2.1 Antibiotic Composition

[0075] The bacteriophage composition of the disclosure are incorporated into a pharmaceutical composition for use in the treatment and/or prevention of psoriasis, skin lesion and bacterial infections caused by bacteria including, but not limited to, Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia, Rhodoferax or a combination thereof. Different phage strains, e.g., as disclosed herein, may be combined with a pharmaceutically acceptable carrier, such as an excipient or stabilizer. Examples of pharmaceutically acceptable carriers, excipients, and stabilizers include, but are not limited to, buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight polypeptides; proteins, such as serum albumin and gelatin; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN^{TM}, polyethylene glycol (PEG), and PLURONICS.TM.. The pharmaceutical compositions of the present invention (e.g., antibacterial compositions) can also include a lubricant, a wetting agent, an emulsifier, a suspending agent, and a preservative, e.g., in addition to the above ingredients.

[0076] The compositions of the present invention may also be combined with one or more non-phage therapeutic and/or prophylactic agents, useful for the treatment and/or prevention of bacterial infections, as described herein and/or known in the art (e.g. one or more antibiotic agents). Other therapeutic and/or prophylactic agents that may be used in combination with the composition of the invention include, but are not limited to, antibiotic agents, anti-inflammatory agents, antiviral agents, local anesthetic agents, growth factors, and corticosteroids. In certain embodiments, the pharmaceutical composition is formulated for treatment and/or prevention of psoriasis, skin lesion or bacterial infections and comprises one or more additional therapeutic and/or prophylactic agents selected from antibiotic agents, local anesthetic agents, and growth factors. In some embodiments, the composition is administered in the absence of an antibiotic agent.

[0077] Standard antibiotics that may be used with pharmaceutical compositions comprising a bacteriophage include, but are not limited to, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, rhodostreptomycin, streptomycin, tobramycin, apramycin, rifamycin, naphthomycin, mupirocin, geldanamycin, ansamitocin, carbacephems, imipenem, meropenem, ertapenem, faropenem, doripenem, panipenem/betamipron, biapenem, PZ-601, cephalosporins, cefacetrile, cefadroxil, cefalexin, cefaloglycin, cefalonium, cefaloridine, cefalotin, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefradine, cefroxadine, ceftezole, cefaclor, cefonicid, cefprozil, cefuroxime, cefuzonam, cefmetazole, cefotetan, cefoxitin, cefcapene, cefdaloxime, cefdinir, cefditoren, cefetamet, cefixime, cefmenoxime, cefteram, ceftibuten, ceftiofur, ceftiolene, ceftizoxime, ceftriaxone, cefoperazone, ceftazidime latamoxef, cefclidine, cefepime, cefluprenam, cefoselis, cefozopran, cefpirome, cefquinome, flomoxef. ceftobiprole, azithromycin, clarithromycin, dirithromycin, erythromycin, roxithromycin, aztreonam, pencillin and penicillin derivatives, actinomycin, bacitracin, colistin, polymyxin B, cinoxacin, flumequine, nalidixic acid, oxolinic acid, piromidic acid, pipemidic acid, rosoxacin, ciprofloxacin, enoxacin, fleroxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin, balofloxacin, gatifloxacin, grepafloxacin, levofloxacin, moxifloxacin, pazufloxacin, sparfloxacin, temafloxacin, tosufloxacin, clinafloxacin, garenoxacin, gemifloxacin, stifloxacin, trovalfloxacin, prulifloxacin, acetazolamide, benzolamide, bumetanide, celecoxib, chlorthalidone, clopamide, dichlorphenamide, dorzolamide, ethoxyzolamide, furosemide, hydrochlorothiazide, indapamide, mafendide, mefruside, metolazone, probenecid, sulfacetamide, sulfadimethoxine, sulfadoxine,

sulfanilamides, sulfamethoxazole, sulfasalazine, sultiame, sumatriptan, xipamide, tetracycline, chlortetracycline, oxytetracycline, doxycycline, lymecycline, meclocycline, methacycline, minocycline, rolitetracycline, methicillin, nafcillin, oxacilin, cloxacillin, vancomycin, teicoplanin, clindamycin, co-trimoxazole, flucloxacillin, dicloxacillin, ampicillin, amoxicillin and any combination thereof in amounts that are effective to additively or synergistically enhance the therapeutic and/or prophylactic effect of a composition of the invention.

[0078] Local anesthetics that may be formulated for use with pharmaceutical compositions disclosed herein include, but are not limited to, tetracaine, tetracaine hydrochloride, lidocaine hydrochloride, dimethisoquin hydrochloride, dibucaine, dibucaine hydrochloride, butambenpicrate, and pramoxine hydrochloride. An exemplary concentration of local anesthetic is about 0.025% to about 5% by weight of the total composition. In some embodiments, the anesthetic agent is formulated in a pharmaceutical composition that is a topical formulation.

[0079] Corticosteroids that may be used with the compositions disclosed herein include, but are not limited to, betamethasone, dipropionate, fluocinolone, actinide, betamethasone valerate, triamcinolone actinide, clobetasol propionate, desoximetasone, diflorasone diacetate, amcinonide, flurandrenolide, hydrocortisone valerate, hydrocortisone butyrate, and desonide. An exemplary concentration of corticosteroid is about 0.01% to about 1% by weight of the total composition.

[0080] The composition comprising bacteriophage may include other agents that are useful for a treating psoriasis. These agents include topical corticosteroid, retinoids, vitamin D analogues, calcipotriol, coal tar, moisturizers and emollients such as mineral oil, phototherapy, dithranol, oil, corticosteroids (i.e. desoximetasone), fluocinonide and retinoids. In certain embodiments, the composition is used in a method in combination with phototherapy.

[0081] Pharmaceutical compositions comprising a bacteriophage can be formulated in a unit dose or multi-dose formulation. In one embodiment, the formulations can be topically applied, e.g., formulations selected from ointments, solutions, and sprays. Other suitable formulations include suspensions, emulsions, extracts, powders, or granules; and additionally may include a dispersing agent or a stabilizing agent.

[0082] The compositions disclosed herein are administered topically (e.g., in the form of a lotion, solution, cream, ointment, or dusting powder), or epi- or transdermally (e.g., by use of a skin patch). In one embodiment, a composition is formulated for topical administration, either as a

single agent, or in combination with other therapeutic and/or prophylactic agents, as described herein or known in the art.

[0083] In certain embodiments, the compositions are formulated for topical administration, e.g., to an area of non-intact skin. Non-intact skin can include, but is not limited to, skin lesions, vesicles, chronic ulcers, cysts, blisters, bullae, open sores such as decubitus ulcers (bed sores) and other pressure sores, cellulitis sores, erysipelas lesions, wounds, burn wounds, or other conditions where the skin is damaged, broken, cracked, breached and/or otherwise compromised. Topical formulations generally include a sterile buffer, such as a sterile PBS, water, or saline buffer, or a sterile SM buffer. One particular SM buffer suitable for use in certain embodiments of the instant invention comprises Tris-HCl, NaCl, and/or $MgSO_47H_2O$, e.g., about 0.05 M Tris-HCl (pH 7.4-7.5), about 0.1 M NaCl, and/or about 10 mM $MgSO_4H_2O$. In other embodiments, the formulation further comprises an SM buffer and 10 mM $MgCl_2$. In still other embodiments, the formulation further comprises an SM buffer and about 20% to about 30% ethanol.

[0084] For topical application to the skin, the compositions may be combined with one or a combination of carriers for topical formulations, which can include, but are not limited to, an aqueous liquid, an alcohol base liquid, a water soluble gel, a lotion, an ointment, a nonaqueous liquid base, a mineral oil base, a blend of mineral oil and petrolatum, lanolin, liposomes, proteins carriers such as serum albumin or gelatin, powdered cellulose carmel, and combinations thereof.

[0085] In certain embodiments, topical pharmaceutical compositions of the invention are provided in a hermetically sealed container. The container may a vial, tube, bottle, ampoule, or the like; and may comprise or consist of glass, plastic, or other suitable material. Ampoules, for example, generally are produced industrially from short lengths of glass tubing, shaped by heating with gas torches and gravity. Computer vision techniques often are employed, e.g., for quality control. The filling and sealing of ampoules may be done by automated machinery. Blank ampoules can be purchased from scientific glass supply houses and sealed, e.g., with a small gas torch, preferably under inert atmospheres. In some embodiments, the container also may be filled with an inert gas, in addition to the pharmaceutical composition. In some embodiments, the composition is provided in an ampoule, or other suitable container, and transferred for use to a vehicle suitable for direct contact with non-intact skin, e.g., a patch, wipe, bandage, dressing, as described below.

[0086] The topical mode of delivery may include a smear, a spray, a bandage, a time-release patch, a liquid-absorbed wipe, and combinations thereof. In certain embodiments, the composition is provided, either directly or in a carrier(s), in a patch, wipe, bandage, dressing, or other vehicle suitable for direct contact with the skin, either intact or non-intact skin.

[0087] In some embodiments, topical administration of a composition comprises use of a dressing. The composition comprising a bacteriophage may be incorporated into a dressing and/or applied separately along with the use of a dressing. A dressing promotes healing by keeping a wound moist, creating a barrier against infection, and/or keeping the surrounding skin dry.

[0088] Modes of administration described herein and/or known in the art may be used to deliver desired dosages of the bacteriophage and in accordance with suitable dosage regimens. Dosages and dosage regimens may vary depending on the particular formulation, route of administration, condition being treated, and other factors. Animal experiments can provide reliable guidance for the determination of effective doses in human therapy, e.g., as within the skill of the ordinary physician. Interspecies scaling of effective doses can be performed by one of ordinary skill in the art following the principles described, e.g., by Mordenti, J. et al. "The use of interspecies scaling in toxicokinetics" in Toxicokinetics and New Drug Development, Yacobi et al., Eds., Pergamon Press, New York 1989, pp 42-96.

[0089] In certain embodiments, the composition is a skin care product. In certain embodiments, the skin care product is a paste, cream, lotion, gel, moisturizer, cleanser, or sunscreen. Examples of a skin care cosmetic dermatological compositions are referenced in U.S. Pub 2016/0235791A1.

[0090] Skin care products may be formulated by combining a present composition and a suitable cosmetic or pharmaceutical vehicle. Non-limiting examples of components conventionally used in skin creams include thickeners; preservatives; lipid-soluble components; methoxycinnamate esters of medium-chain alcohols; benzophenone-3; fragrance; complexes of polyacrylamide, C_{13}-C_{14} isoparaffin, laureth-7, and water; and colorings. The concentrations of individual components present may vary widely, but often range from about 0.01% to about 10%, more usually from about 0.05% to about 5% (w/w).

[0091] Non-limiting examples of thickeners xanthan gum, carrageenan, and combinations thereof. Non-limiting examples of preservatives include methylparaben; butylparaben; propylparaben; a complex of propylene glycol, phenoxyethanol, chlorphenesin, and methylparaben; and combinations thereof. Suitable preservatives are commercially available.

[0092] The skin care product may also include lipid-soluble component(s) that provide smoothness. Non-limiting examples of lipid-soluble components include steareth-2; steareth-21; dimethicone; and branched-chain neopentanoate ester selected from the group consisting of octyldodecyl neopentanoate, heptyldodecyl neopentanoate, nonyldodecyl neopentanoate, octylundecyl neopentanoate, heptylundecyl neopentanoate, nonylundecyl neopentanoate, octyltridecyl neopentanoate, heptyltridecyl neopentanoate, and nonyltridecyl neopentanoate. Steareth-2 is polyoxyethylene stearylether with 0.01% butylated hydroxyanisole and 0.005% citric acid added as preservatives. Steareth-21 is polyoxyethylene stearylether with 0.01% butylated hydroxyanisole and 0.005% citric acid added as preservatives.

[0093] Other components that may be present include benzophenone-3, which screens out ultraviolet rays. The composition also may include a variety of other components such as coloring agents, fragrance, and the like.

[0094] In some cases, the pH of the formulation may be adjusted with acceptable acids, bases or buffers. The compositions also may contain diluents commonly used in the art such as water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylsulfoxide (DMSO) dimethylformamide, oils, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0095] In certain embodiments, the skin care product is provided in a liquid or semisolid form (e.g., liquid, paste, gel, cream, lotion, etc.) for topical application. In certain embodiments, the skin care product may be applied topically to reduce inflammation, redness, or irritation. For example, the skin care product may be topically administered to treat an autoimmune and/or dermatological condition such as acne, psoriasis, and/or rosacea.

5.3 Patient Population

[0096] In some embodiments, a subject treated for psoriasis, skin lesion or infection in accordance with the methods provided herein is a human who has or is diagnosed with a disorder. In other embodiments, a subject treated for the disorder in accordance with the methods provided herein is a human predisposed or susceptible to the disorder. In some embodiments, a subject treated for the disorder in accordance with the methods provided herein is a human at risk of developing the disorder.

[0097] In one embodiment, a subject treated for psoriasis, skin lesion or infection in accordance with the methods provided herein is a human infant. In another embodiment, the subject is a human toddler. In another embodiment, a subject treated for infection in accordance with the methods provided herein is a human child. In another embodiment, a subject is a human adult. In another embodiment, a subject is a middle-aged human. In another embodiment, a subject is an elderly human. In some embodiments, the subject treated in accordance with the methods provided herein that has a recurrence of a bacterial infection.

[0098] In certain embodiments, a subject treated for the disorder in accordance with the methods provided herein is a human that is about 1 to about 5 years old, about 5 to 10 years old, about 10 to about 18 years old, about 18 to about 30 years old, about 25 to about 35 years old, about 35 to about 45 years old, about 40 to about 55 years old, about 50 to about 65 years old, about 60 to about 75 years old, about 70 to about 85 years old, about 80 to about 90 years old, about 90 to about 95 years old or about 95 to about 100 years old, or any age in between. In a specific embodiment, a subject treated for the disorder in accordance with the methods provided herein is a human that is 18 years old or older. In a particular embodiment, a subject treated for the disorder in accordance with the methods provided herein is a human child that is between the age of 1 year old to 18 years old. In a certain embodiment, a subject treated for the disorder in accordance with the methods provided herein is a human that is between the age of 12 years old and 18 years old. In a certain embodiment, the subject is a male human. In another embodiment, the subject is a female human. In one embodiment, the subject is a female human that is not pregnant or is not breastfeeding. In one embodiment, the subject is a female that is pregnant or will/might become pregnant, or is breast feeding.

[0099] In some embodiments, a subject treated for the disorder in accordance with the methods provided herein is administered a pharmaceutical composition thereof, or a combination therapy before any adverse effects or intolerance to therapies.

[00100] In some embodiments, a subject treated for the disorder in accordance with the methods provided herein is a human that has established resistance to previous antibiotic therapies other than treatment with the presently disclosed therapy. In certain embodiments, a subject treated for infection in accordance with the methods provided herein is a human already receiving one or more conventional antibacterial therapies. Among these patients are patients who have developed infections that are resistant to antibiotics and patients with recurring infections despite treatment with existing therapies.

5.6 Kits

[00101] Also provided are kits for use in methods of treatment of psoriasis, skin lesion or a bacterial infection. The kits can include a bacteriophage or composition provided herein, a second agent or composition, and instructions providing information to a health care provider regarding usage for treating the disorder. Instructions may be provided in printed form or in the form of an electronic medium such as a floppy disc, CD, or DVD, or in the form of a website address where such instructions may be obtained. A unit dose of a bacteriophage or composition provided herein, or a second agent or composition, can include a dosage such that when administered to a subject, a therapeutically or prophylactically effective dose of the bacteriophage or composition can be maintained in the subject for at least 1 days. In some embodiments, a bacteriophage or composition can be included as a sterile aqueous pharmaceutical composition or dry powder (e.g., lyophilized) composition. In some embodiments, suitable packaging is provided. As used herein, "packaging" includes a solid matrix or material customarily used in a system and capable of holding within fixed limits a bacteriophage provided herein and/or a second agent suitable for administration to a subject. Such materials include glass and plastic (e.g., polyethylene, polypropylene, and polycarbonate) bottles, vials, paper, plastic, and plastic-foil laminated envelopes and the like. If e-beam sterilization techniques are employed, the packaging should have sufficiently low density to permit sterilization of the contents.

[00102] The kits described herein contain one or more containers, which contain bacteriophage as described. The kits also contain instructions for mixing, diluting, and/or administrating the compounds. The kits also include other containers with one or more solvents, surfactants, preservative and/or diluents (e.g., normal saline (0.9% NaCl), or 5% dextrose) as well as containers for mixing, diluting or administering the components to the sample or to the patient in need of such treatment.

[00103] The compositions of the kit may be provided as any suitable form, for example, as liquid solutions or as dried powders. When the composition provided is a dry powder, the powder may be reconstituted by the addition of a suitable solvent, which may also be provided. In embodiments where liquid forms of the composition are sued, the liquid form may be concentrated or ready to use. Suitable solvents for drug compositions are well known and are available in the literature. The solvent will depend on the agent and the mode of use or administration.

[00104] The kits comprise a carrier being compartmentalized to receive in close confinement one or more container such as vials, tubes, and the like, each of the container comprising one of the separate elements to be used in the method. For example, one of the container may comprise a positive control in an assay. Additionally, the kit may include containers for other components, for example, buffers useful in the assay.

5.7 Methods of Treatment and Prevention

[00105] Another aspect of the present disclosure relates to the use of the composition in preventing and/or treating psoriasis, skin lesion and bacterial infection. In certain embodiments, the subject receiving a pharmaceutical composition of the invention is a mammal (e.g., bovine, ovine, caprine, equid, primate (e.g., human), rodent, lagomorph or avian (e.g., chicken, duck, goose)). In certain embodiments, the subject receiving a pharmaceutical composition of the invention is a human, and particularly a patient that suffers from or is at risk of suffering from psoriasis, skin lesion and bacterial infection. In the context of the present invention, "treatment" refers to obtaining a therapeutic benefit in a subject receiving the pharmaceutical composition. With respect to achieving a therapeutic benefit, the object is to eliminate, lessen, manage, decrease the severity of, prevent worsening, ameliorate, or slow the progression of the symptoms

or underlying cause (e.g., bacterial infection) associated with the pathological condition or disorder. It is also contemplated that the composition, in certain embodiments, may act as a prophylactic or preventative measure, preventing the onset of psoriasis, skin lesion and infection caused by one or more bacteria. "Prevention" refers to obtaining a prophylactic benefit in a subject receiving the composition. With respect to achieving a prophylactic benefit, the object is to delay or prevent the symptoms or underlying cause (e.g., bacterial infection) associated with the pathological condition or disorder.

[00106] The composition disclosed herein has activity against a plurality of bacterial strains. In certain embodiments, the composition has activity against a plurality of strains of Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia or Rhodoferax. Accordingly, another aspect of the invention provides methods of treating and/or preventing psoriasis, skin lesion and infections associated with a plurality of strains of Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia or Rhodoferax in both humans and animals using the composition. In other aspects, the invention provides methods of treating and/or preventing infections associated with related species or strains of these bacteria. In some particularly preferred embodiments, the bacterial infection is an infection associated with psoriasis.

[00107] The compositions of the invention comprises a therapeutically and/or prophylactically effective amount of one of more bacteriophage strains, as described herein. A therapeutically and/or prophylactically effective amount refers to an amount required to bring about a therapeutic and/or prophylactic benefit, respectively, in a subject receiving said amount. A therapeutically and/or prophylactically effective amount will depend on the particular formulation, route of administration, condition being treated, whether other agents or therapies are used in combination with methods of the invention, and other factors.

[00108] In some specific embodiments, the compositions disclosed herein are formulated as pharmaceutical compositions for use in treating and/or preventing bacterial infections associated with areas of non-intact skin. The therapeutically and/or prophylactically effective amount will depend on the area of non-intact skin and the pharmaceutical compositions can be formulated to reflect same. For example, in some preferred embodiments, the pharmaceutical

composition comprises phage strains where each is present in an amount corresponding to about 10^3 to about 10^{13} phage particles/cm^2 of said area. In certain embodiments, the therapeutic and/or prophylactic amount may correspond to at least about 10^4, at least about 10^5, at least about 10^6, at least about 10^7, at least about 10^8, or at least about 10^9, phage particles/cm^2 of the area of non-intact skin to be treated. In certain embodiments, the therapeutic and/or prophylactic amount may correspond to less than about 10^{13}, less than about 10^{12}, less than about 10^{11}, less than about 10^{10}, less than about 10^9, or less than about 10^8 phage particles/cm^2 of the area of non-intact skin to be treated. In certain embodiments, each phage strain is present in the pharmaceutical composition in an amount corresponding to 10^7 to 10^9 phage particles/cm^2 of the non-intact skin area.

[00109] In some embodiments, administration of a therapeutically effective amount of a composition, in accordance with the instant invention, results in improved clearing of psoriasis, such as a reduction in the area of psoriatic skin compared to the area before initiation of treatment. The area can be expressed as a percentage of the initial psoriatic skin area, at one or more time points after initiation of treatment. For example, in some preferred embodiments, psoriatic skin area decreases by about 20-30%, about 30-40%, about 40-50%, about 50-60%, about 60-70%, about 70-80%, about 80-90%; or about 90-99% over a course of treatment with a composition of the invention. In certain embodiments, the decrease in psoriatic skin area occurs at least by day 1 after treatment initiation (t1), day 2 after treatment initiation (t2), day 3 after treatment initiation (t3), day 4 after treatment initiation (t4), day 5 after treatment initiation (t5), day 6 after treatment initiation (t6), day 7 after treatment initiation (t7), day 8 after treatment initiation (t8), day 9 after treatment initiation (t9), day 10 after treatment initiation (t10), day 12 after treatment initiation (t12), day 15 after treatment initiation (t15), day 20 after treatment initiation (t20), day 25 after treatment initiation (t25), or day 30 after treatment initiation (t30). In a particularly preferred embodiment, the psoriatic skin area is reduced by about 30% to about 40%, by at least day 9 after treatment initiation (t9). In a further particularly preferred embodiment, psoriatic skin area is reduced by about 40% to about 50%, by at least day 9 after treatment initiation (t9). In still a further particularly preferred embodiment, wound area is reduced by about 50% to about 60%, by at least day 9 after treatment initiation (t9). In an even more particularly preferred embodiment, psoriatic skin area is reduced by about 60% to about 70%, by at least day 9 after treatment initiation (t9).

[00110] In certain embodiments, a composition disclosed herein is used as a single agent for treating or preventing infections caused by Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia, Rhodoferax or a combination thereof. In other embodiments, the disclosed composition is used in further combination with other agents, including other bacteriophage (for example, that target a different species or strain of bacteria), or with antibiotics that target the same or different kinds of bacteria, including bacteria selected from any gram-positive bacteria, any gram-negative bacteria, and any other groups of bacteria that is not classified as gram-positive or gram-negative. The compositions of the invention may also be used in combination with any other means of treating psoriasis, skin lesion or infection known to one of skill in the art.

[00111] In some embodiments, the composition according to the invention is used in combination with at least one phage strain against the same or a different bacteria species. In certain embodiments, the composition is used in combination with at least one phage strain selected from the group consisting of bacteriophage strain Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia, Rhodoferax or a combination thereof.

[00112] In certain embodiments, the composition is applied topically to reduce inflammation, redness, and/or irritation, and/or to improve the appearance of the skin. In other embodiments, the composition is applied topically to treat an autoimmune and/or dermatological condition such as acne, psoriasis, and/or rosacea. In certain embodiments, provided herein is a method of treating or preventing psoriasis, skin lesion and bacterial infection by administering a composition comprising one or more strains of bacteriophage provided herein. The method comprises contacting a subject with a composition comprising one or more species of bacteriophage as described herein in an amount effective to prevent or treat the subject. Provided herein are methods for treating or preventing psoriasis, skin lesion, or a bacterial infection in a subject by administering to a subject in need thereof the composition described herein in an amount effective to reduce the symptoms.

5.8 Diagnostic/Predictive Tests of the Invention

[00113] The disclosure also relates to a method of predicting or determining the efficacy of a bacteriophage therapy in a subject, wherein the method comprises a step of determining a lytic activity of one or more strains of bacteriophage Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia, Rhodoferax or a combination thereof from a sample from said subject, such a lytic activity being indicative of an efficient treatment. In one aspect, the method further optionally comprises a step of treating said subject by one or more bacteriophages having a lytic activity to one or more strains of bacteriophage Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia, Rhodoferax or a combination thereof from a sample of said subject.

[00114] In another aspect, the invention provides a method for selecting a subject or determining whether a subject is susceptible to benefit from a bacteriophage therapy, wherein the method comprises the step of determining a lytic activity of one or more bacteriophages strains of Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia, Rhodoferax or a combination thereof from a sample of said subject, a lytic activity of one or more bacteriophages to at least one strain indicating a responder subject.

[00115] Another object of the invention relates to a method for predicting the response of a subject to a bacteriophage therapy, wherein the method comprises the step of determining a lytic activity of one or more bacteriophage strain Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia, Rhodoferax or a combination from a sample of said subject, a lytic activity of one or more bacteriophage of the invention to at least one strain being indicative of a good response to said therapy.

[00116] The following Examples illustrate the synthesis and use of representative compositions provided herein. These examples are not intended, nor are they to be construed, as limiting the scope of the claimed subject matter. It will be clear that the scope of subject matter may be practiced otherwise than as particularly described herein. Numerous modifications and variations of the subject matter are possible in view of the teachings herein and, therefore, are within the scope the claimed subject matter.

6. EXAMPLES

[00117] 6.1 Study participants and study design

[00118] Eligible participants with psoriasis were recruited from the FAMILY cohort, a population-representative sample by Leung et al and the Hong Kong psoriasis patients association (Leung et al 2017). Family controls living in the same household as the participants with psoriasis were recruited. Lesional skin samples from four different locations (elbow, forearm, knee, and scalp) were obtained from eligible participants with psoriasis. Healthy skin samples were collected at contralateral non-lesional sites as well as matching skin sites from family controls.

[00119] This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority HK West Cluster (project UW-085). All study participants were well informed about the study and provided written informed consent.

[00120] Inclusion Criteria

[00121] All participants were age from 18 years to 75 years at the time of enrolment and were willing to provide skin swab specimens. Eligible participants with psoriasis were experienced lesion at least one location of elbow, forearm, knee or scalp, and were non-lesional at the contralateral site of the lesional location. Eligible family controls were subjects without psoriasis.

[00122] Exclusion Criteria

[00123] Subjects with any antibiotic treatment (systemic or topical) within one month before the study were excluded.

[00124] Skin microbiome sampling

[00125] Swabs were collected from all eligible participants with psoriasis and family controls using eSwab (Copan Diagnostics). Each skin sample was taken by swabbing back and forth for 25 times. The swabbing area was approximately equal to the area of a circle with a radius of 2 centimeters.

[00126] DNA extraction and sequencing

[00127] Genomic DNA was extracted from each sample using QIAamp DNA Mini isolation kit (QIAGEN) following the manufacturer's instructions for swabs. DNA library was prepared by KAPA Hyper Prep kit. Shotgun sequencing was performed using Illumina HiSeq 1500 platform (2 x 100 bp paired-end sequencing).

[00128] **Microbiome Operational Taxonomic Unit (OTU) Classification**

[00129] Adapters and human contaminate were removed from raw sequences. IDBA-UD was used to *de novo* assemble reads after the quality control into contigs. Bacterial OTU was classified through DIAMOND and MEGAN. Relative abundance (%) of normalized OTU reads count from MEGAN was used as the estimation of bacterial abundance. Phage OTU was mined through VirSorter from assembled contigs of all samples. Non-redundant contigs with length ≥ 10kb or circular (Roux et al 2017) and ranked as *category one* ("most confident" predictions) by VirSorter were defined as phage OTU. Phage taxonomy was annotated by BLAST (e value cut-off 10^{-5}, hit with the highest bit-score) search against NCBI viral RefSeq database (v69, 2015-02). Phage abundance was estimated by reads count mapped to phage contigs and normalized by the length of contig and total reads of each sample. Reads mapped to contigs annotated as *Enterobacteria phage phiX174 sensu lato*, a contamination of Illumina data in *de novo* assembly were removed (Mukherjee et al 2015).

[00130] **Statistical Analyses**

[00131] Statistical analysis and visualization were conducted using R statistical software (R, version 3.3.3, R Development Core Team). The median of microbiome OTU abundance across all skin samples was used to rank the top most abundant OTU. Diversity indexes were analyzed using the vegan package (version 2.4-4). Alpha diversity was assessed using Shannon Diversity Index to quantify both species richness (the number of different species found in a site) and evenness (how evenly different species distributed in a site). Beta diversity that measures the dissimilarity in the composition of microbial community was estimated by Principal Coordinate Analysis (PCoA) from Bray-Curtis distances based on microbiome OTU abundance across all samples. Microbiome data was visualized through ggplot2 package (version 2.2.1).

[00132] To adjust the effect of household and paired contralateral skin samples from the same subject, linear mixed effect model was used to test the difference of microbial diversity measures and relative abundance between psoriasis lesional skin vs healthy skin (contralateral

non-lesional skin and family controls). The groups of samples (lesional skin vs healthy skin) was the fixed effect in the model, and the household was the random effect with the indication of samples from which subject (patient vs family control) in the same household as the random slope. Sex was added as another fixed effect in the linear mixed model to test the effect of sex to skin microbiome composition. Linear mixed effect modeling was performed and p-values of fixed effects were estimated. For the test of differentially abundant microbiome OTU, dominate phage species (top ten most abundant phages) and bacterial species (relative abundance $\geq 0.1\%$) were considered and adjusted for multiple comparisons. A two-sided non-parametric Jonckheere-Terpstra test with 5000 permutations was applied as sensitivity analysis to investigate the trend found in lesional skin and healthy skin as ordered by lesional skin, followed by contralateral non-lesional skin and family controls skin. To study the phage-host relationship, samples were divided into two groups based on the level of phage abundance (low vs high). Phage abundance between 0 to 50 percent of the maximum was defined as low, and above 50% of the maximum was defined as high. Host bacteria genus with median relative abundance $\geq 1\%$ was analyzed. The difference of host bacteria abundance between low vs high phage levels was tested by two-sample t-test.

[00133] Results

[00134] Table 1. Background Characteristics of Study Participants

Characteristic	Patients with psoriasis		Family Controls
Total subjects	16		16
Skin samples collected and analyzed	27 Lesional	54 Healthy	
Location of skin samples collected	Elbow (n=7) Forearm (n=7) Knee (n=5) Scalp (n=8)	Contralateral Elbow (n=7) Contralateral Forearm (n=7) Contralateral Knee (n=5) Contralateral Scalp (n=8)	Elbow (n=7) Forearm (n=7) Knee (n=5) Scalp (n=8)
Age, mean (SD), y	53.4 (12.2)		51.2 (10.1)
Female, No. (%)	5 (31)		13 (81)
Asian race/ethnicity, No. (%)	16 (100)		16 (100)

BMI, mean (SD)	22.6 (3.8)	22.8 (3.25)
SAPASI Index, mean (SD)	11.2 (10.0)	NA

[00135] Abbreviations: BMI, body mass index; SAPASI, self-administered psoriasis area and severity index.

[00136] 16 patients with psoriasis and 16 family controls living in the same households were included in the study. In total, 81 skin microbiome samples were collected (27 lesional skin from patients with psoriasis, and 54 healthy skin including contralateral non-lesional skin and family controls skin) from four different locations (Table 1). Distribution of age and BMI for patients and family controls did not differ (two-sample t-test, P = .59 for age; P = .87 for BMI). Although distribution of sex was different between patients and family controls (chi-square test, P = .004), sex did not significantly affect the skin microbiome composition for phage species community (FIG. 8A and FIG. 9A). PCoA1 estimated beta-diversity had insignificant difference between female and male samples (linear mixed effect model, P = .16). Bacterial species microbiome composition was also not significantly influenced by the sex effect (FIG. 8B and FIG. 9B). PCoA1 estimated beta-diversity was not significantly different in female samples compared to male samples (linear mixed effect model, P = .78).

[00137] Both phage component and bacteria component were characterized to assess the association between cutaneous microbiome and psoriatic skin lesions. Figure 1 shows the distribution of top ten most abundant species ranked by the median abundance among all skin samples in phage community composition and bacterial community composition (order of top abundant phage species and bacterial species are listed in the FIG. 5 and FIG. 6). *Salmonella phage vB_SenS-Ent2, Rhodoferax phage P26218*, and *Mycobacterium phage DrDrey* were the three most abundant phage species in all samples. *Pseudomonas species, Acinetobacter species*, and *Cutibacterium acnes* were the three most abundant bacterial species in all samples.

[00138] Shannon Diversity Index was used to quantify the alpha diversity of microbial species. The phage species alpha diversity (FIG. 10A) was not significantly different (linear mixed effect model, P = .62) between lesional skin (median [Q1-Q3] 2.93 [2.87-3.05]) and healthy skin (median [Q1-Q3] 2.93 [2.87-3.00]). On the other hand, the bacterial species alpha diversity (FIG. 10B) was significantly higher (linear mixed effect model, P < .001) for healthy

skin (median [Q1-Q3] 3.65 [3.22-4.03]) than lesional skin (median [Q1-Q3] 2.85 [2.41-3.03]). Sex of samples did not significantly influence the alpha diversity for both phage species and bacterial species (linear mixed effect model with locations as the fixed effect, P = .97 for phage, P = .77 for bacteria).

[00139] The association between the composition of microbial community and psoriatic skin lesions was investigated through microbiome beta diversity. Beta diversity of phage species community and bacterial species community was illustrated with PCoA plots (FIG. 11A for phage, FIG. 11B for bacteria). Figure 2 displays the comparison of the microbiome beta diversity as measured by the primary principal coordinate (PCoA1) between lesional skin and healthy skin. PCoA1 of phage species beta diversity (Figure 2A) was significantly different (linear mixed effect model, P < .05) in lesional skin (median [Q1-Q3] -0.0015 [-0.051-0.21]) compared to healthy skin (median [Q1-Q3] -0.070 [-0.21-0.017]). Also, PCoA1 of bacterial species beta diversity (Figure 2B) was significantly different (linear mixed effect model, P <.001) between lesional skin (median [Q1-Q3] 0.076 [-0.0049-0.18]) and healthy skin (median [Q1-Q3] -0.058 [-0.23-0.096]).

[00140] Figure 3 shows the difference of the abundance for the top ten most abundant phage species between lesional skin and healthy skin. The top ten most abundant phage species were significantly more abundant in healthy skin than lesional skin (linear mixed effect model, FDR adjusted P < .05). *Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2,* and *Bacillus phage SP-10* were the top three. We further tested whether the abundance difference is ordinal with lesional skin as the lowest, contralateral non-lesional skin as intermediate and family controls skin as the highest. The ordered differences were significant for these phages (Jonckheere-Terpstra test, FDR adjusted P < .05). Details of the results of testing on the differentially abundant phage species were provided in FIG. 7.

[00141] The ten most abundant phage species with abundant host bacteria genus (median relative abundance > 1%) were further investigated to understand the phage-host relationship. Two phage species, *Acinetobacter phage Presley* with host bacteria *Acinetobacter* (relative abundance, median [Q1-Q3] 2.92 [0.93-14.35]), and *Pseudomonas phage O4* with host bacteria *Pseudomonas* (relative abundance, median [Q1-Q3] 3.44 [0.50-11.20]) were selected. Notably, two phage species showed the capability to suppress the abundance of their host bacteria at the

high level of abundance (definition of high vs low level of phage abundance described in Methods). The cutoffs for high vs low for *Acinetobacter phage Presley* and *Pseudomonas phage O4* was 3.35 and 1.74, respectively. As shown in Figure 4A, subjects with high level of *Acinetobacter phage Presley* had significantly lower (two-sample t-test, P = .029) abundance of host bacteria *Acinetobacter* than subjects with low level of the phage. The abundance of host bacteria *Pseudomonas* was significantly lower (two-sample t-test, P < .001) in subjects with high level of *Pseudomonas phage O4*, comparing with subjects with low level of *Pseudomonas phage O4*.

[00142] **Discussion**

[00143] In this study, we provide a comprehensive investigation of the phage composition of skin microbiota at species resolution in psoriasis. The most important findings are the differences between phage species composition in lesional and healthy skin, and the discovery of two abundant phage species that inhibits host bacteria. The difference in lesional skin of psoriasis patients compared with healthy skin of contralateral sites and family controls indicate that the alteration of the composition of phage community plays a role in the health status of the skin in psoriasis. Two significantly differential abundant phage species between psoriasis lesional skin and healthy skin, *Acinetobacter phage Presley* and *Pseudomonas phage O4,* also demonstrate the capability in suppressing the abundance of their host *Acinetobacter* and *Pseudomonas*. Our novel finding informs us of the strong ties between the skin phage community and the skin bacterial community in psoriasis.

[00144] A significant difference in the composition of phage species (beta diversity) between psoriasis lesional skin and healthy skin was found, and the composition of bacterial species was also significantly different between the two. The observed differences in microbiome composition for both phage and bacterial species implied the alteration of microbial community was associated with psoriatic skin lesions. Several studies previously demonstrated the impact of skin microbiota on the immune homeostasis. Naik et al found that defined skin commensal bacteria, especially *Staphylococcus epidermidis*, could enhance the skin barrier to defend against pathogen invasion as well as influence the level of cytokine IL-17 which contributed to the skin inflammation disorders including psoriasis (Naik et al 2015). Another

study also reported skin microbiota enhanced immune responses to pathogen and *Staphylococcus epidermidis* could accelerate the wound healing process (Linehan et al 2018). These studies provided an explanation to our observed difference in microbial composition between psoriasis lesional skin and healthy skin. They also sparked interest in finding beneficial topical bacterial probiotics that could help maintain a healthy skin.

[00145] We also observed a significantly decreased bacterial species alpha diversity measured by Shannon Diversity Index in lesional skin than healthy skin. A reduced bacterial alpha diversity on lesional skin than control skin was previously reported in study of psoriasis (Fahlén et al. 2012, Aleksyenko et al 2013) and other types of skin disorder (Clausen et al 2017, Ring et al 2018). Our finding confirmed the link between a balanced bacterial community and healthy skin. Since the Shannon Diversity Index assessed both how many different species existed (richness) and how evenly different species distributed (evenness), the decreased bacterial species alpha diversity in psoriasis lesional skin might suggest a potential impaired bacterial community (dysbiosis) in psoriasis lesional skin. Yet, no difference was observed in phage species alpha diversity between psoriasis lesional skin and healthy skin. The similarity of phage species alpha diversity could be a result of having only 35 category one phage species, a relatively low number compared with bacterial species.

[00146] In this study, we further extend previous therapeutic angle of probiotic bacteria in treating skin disorder with the possibility of using phages as ingredients for topical probiotics in psoriasis. We found the top ten most abundant phage species across samples were also differentially abundant in lesional skin from patients with psoriasis compared with healthy skin from contralateral sites and family controls. Interestingly, for these top ten most abundant phage species, phage species were more abundant in healthy skin than lesional skin. Significant ordinal Jonckheere-Terpstra test results further confirmed the direction of increasing abundance with lesional skin as the lowest, contralateral non-lesional skin as intermediate and family controls skin as the highest. This observation of higher prevalence of abundant phage species in healthy skin than lesional skin could be related to the state of dysbiosis for lesional skin relative to healthy skin as well as the potential influence of phage on the bacterial composition.

[00147] Another important finding is that high level of two phage species, *Acinetobacter phage Presley* and *Pseudomonas phage O4,* could significantly limit the abundance of their host

bacterial genera *Acinetobacter* and *Pseudomonas*, respectively. Notably, *Acinetobacter baumannii and Pseudomonas aeruginosa in the bacterial genera are known as notorious opportunistic pathogens that may induce skin infection* (Guerrero et al 2010, Wu et al 2011). Facing the multidrug-resistance of *Acinetobacter baumannii and Pseudomonas aeruginosa, researchers have begun to examine the potential of phage therapy for infections.* Regeimbal et al found a cocktail of five phages (phages AB-Army1 and AB-Navy1–4) could promote the healing of wound infection caused by *Acinetobacter baumannii* in mice model (Regeimbal et al 2016). A single phage species *phage PA709* was reported to be able to monitor the *Pseudomonas aeruginosa induced wound infection (Vieira 2012). Two phage species in our study, Acinetobacter phage Presley* and *Pseudomonas phage O4*, could be considered as part of a cocktail of phage-based therapeutic probiotic to facilitate the recovery process to healthy skin from lesional state.

[00148] Conclusions

[00149] This study goes beyond previous bacteria-focused skin microbiota research and examines the bacteriophage at species level the skin microbiome in patients with psoriasis and healthy family controls. The observed difference in the composition of phage species between psoriatic lesional skin and healthy skin suggests an association between phage species and psoriatic lesions. Moreover, two abundant and significant phage species have been shown to suppress host bacteria tied to lesional skin. This paves way for the development of probiotic phage therapies for skin health in psoriasis. Future studies should be conducted to understand the role of phage in the skin microbiota for the treatment and prevention of skin disease or infection.

[00150] Those skilled in the art will recognize or ascertain many equivalents to the specific embodiments of the invention described herein using no more than routine experimentation. Such equivalents are intended to be encompassed by the following claims.

[00151] All publication, patents and patent applications mentioned in this specification are incorporated herein by reference in their entireties into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

[00152] Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

[00153] References

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CLAIMS

What is claimed is:

1. A composition comprising one or more bacteriophage strains selected from Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Bacillus phage SP-10, Pseudomonas phage O4, Haemophilus phage Aaphi23, Enterobacteria phage SfI, Bordetella virus BPP1, Mycobacterium phage DrDrey, Burkholderia virus BcepC6B, Rhodoferax phage P26218, Burkholderia virus phi1026b, Idiomarinaceae phage Phi1M2-2, Ralstonia phage RSK1, Sulfitobacter phage NYA-2014a, Thalassomonas phage BA3, Pseudomonas phage KPP25, Pseudomonas phage NP1, and Pseudomonas virus F116, or a variant thereof, said variant having at least about 80% sequence identity to NCBI accession Nos: YP_009007647.1(Acinetobacter phage Presley), YP_009009926.1(Salmonella phage vB_SenS-Ent2), YP_007003398.1(Bacillus phage SP-10), YP_009304497.1(Pseudomonas phage O4), NP_852738.1(Haemophilus phage Aaphi23), YP_009147451.1(Enterobacteria phage SfI), NP_958679.1(Bordetella virus BPP1), YP_008409492.1(Mycobacterium phage DrDrey), YP_024932.1(Burkholderia virus BcepC6B), and YP_009222582.1 (Rhodoferax phage P26218), NP_945032.1(Burkholderia virus phi1026b), YP_009104301.1(Idiomarinaceae phage Phi1M2-2), YP_008853829.1(Ralstonia phage RSK1), YP_009146206.1(Sulfitobacter phage NYA-2014a), YP_001552271.1(Thalassomonas phage BA3), YP_009030589.1(Pseudomonas phage KPP25), YP_009285843.1(Pseudomonas phage NP1), and YP_164304.1(Pseudomonas virus F116), respectively.

2. The composition of claim 1 wherein the bacteriophage shows antibacterial activity against at least one of Acinetobacter, Salmonella, Bacillus, Pseudomonas, Haemophilus, Enterobacteria, Bordetella, Mycobacterium, Burkholderia or Rhodoferax.

3. The composition of claim 1 wherein the composition comprises bacteriophage strain selected from Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Pseudomonas phage O4, Pseudomonas phage KPP25, Pseudomonas phage NP1, and Pseudomonas virus F116, or a variant thereof, said variant having at least about 80% sequence identity to NCBI accession Nos: YP_009007647.1(Acinetobacter phage Presley), YP_009009926.1(Salmonella phage vB_SenS-Ent2), YP_009304497.1(Pseudomonas phage O4), YP_009030589.1(Pseudomonas phage KPP25), YP_009285843.1(Pseudomonas phage NP1), YP_164304.1(Pseudomonas virus

F116), or at least 50% sequence coverage and 70 % sequence identity to SEQ ID NO:01 and 02, respectively.

4. The composition of claim 3 wherein the bacteriophage shows antibacterial activity against at least one of Acinetobacter, Salmonella or Pseudomonas.

5. The composition of claim 1 wherein the composition comprises bacteriophage strain selected from Acinetobacter phage Presley and Pseudomonas phage O4, Pseudomonas phage KPP25, Pseudomonas phage NP1, Pseudomonas virus F116, or a variant thereof, said variant having at least about 80% sequence identity to NCBI accession Nos: YP_009007647.1(Acinetobacter phage Presley), YP_009304497.1(Pseudomonas phage O4), YP_009030589.1(Pseudomonas phage KPP25), YP_009285843.1(Pseudomonas phage NP1), YP_164304.1(Pseudomonas virus F116), or at least 50% sequence coverage and 70 % sequence identity to SEQ ID NO:01 and 02, respectively.

6. The composition of claim 5 wherein the bacteriophage shows antibacterial activity against at least one of Acinetobacter or Pseudomonas.

7. A pharmaceutical composition comprising the composition of any one of claims 1-6; and a pharmaceutically acceptable carrier.

8. A dermatological composition comprising the composition of any one of claims 1-6.

9. The pharmaceutical composition of claim 7 further comprising an antibiotic agent or an agent for treating psoriasis.

10. A method of treating or preventing psoriasis in a subject comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition according to any one of claims 1-6.

11. The method of claim 10 wherein the psoriasis is associated with an area of intact skin.

12. The method of claim 10 wherein the psoriasis s associated with an area of non-intact skin.

13. The method of claim 10 wherein the pharmaceutical composition is administered topically to the subject.

14. The method of claim 13 wherein the pharmaceutical composition is administered to the subject's elbow, forearm, knee and scalp.

15. The method of claim 10 wherein the pharmaceutical composition is administered to a subject at a skin area with lesion.

16. A method of cosmetic treatment comprising a step of applying on a subject the dermatological composition of claim 8.

17. A method for improving condition of a subject's skin by modifying the microbiome in the subject comprising the step of contacting the subject's skin with the composition of claim 8.

18. The method of claim 16 or 17 wherein the dermatological composition is administered to a subject at a skin area without lesion.

19. The method of claim 16 or 17 wherein the dermatological composition is administered to a subject at a skin area with lesion.

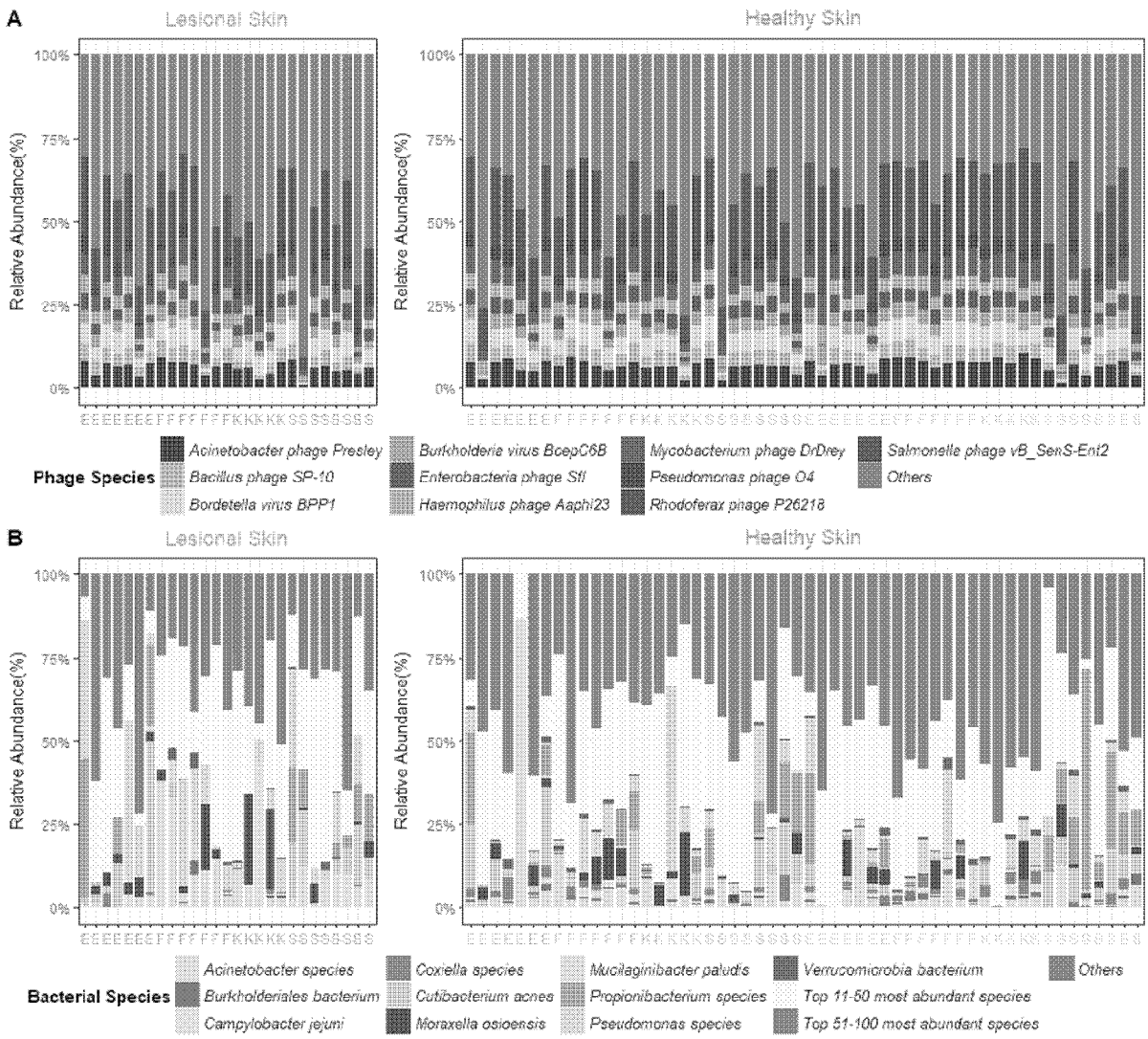
20. A method for preparing a composition comprising producing at least one bacteriophage strain selected from the group consisting of Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Bacillus phage SP-10, Pseudomonas phage O4, Haemophilus phage Aaphi23, Enterobacteria phage SfI, Bordetella virus BPP1, Mycobacterium phage DrDrey, Burkholderia virus BcepC6B, Rhodoferax phage P26218, Burkholderia virus phi1026b, Idiomarinaceae phage Phi1M2-2, Ralstonia phage RSK1, Sulfitobacter phage NYA-2014a, Thalassomonas phage BA3, Pseudomonas phage KPP25, Pseudomonas phage NP1, and Pseudomonas virus F116, or a variant thereof, said variant having at least about 80% sequence identity to NCBI accession Nos:YP_009007647.1(Acinetobacter phage Presley), YP_009009926.1(Salmonella phage vB_SenS-Ent2), YP_007003398.1(Bacillus phage SP-10), YP_009304497.1(Pseudomonas phage O4), NP_852738.1(Haemophilus phage Aaphi23), YP_009147451.1(Enterobacteria phage SfI), NP_958679.1(Bordetella virus BPP1), YP_008409492.1(Mycobacterium phage DrDrey), YP_024932.1(Burkholderia virus BcepC6B), and YP_009222582.1(Rhodoferax phage P26218), **NP_945032.1(Burkholderia virus phi1026b), YP_009104301.1(Idiomarinaceae phage Phi1M2-2), YP_008853829.1(Ralstonia phage RSK1), YP_009146206.1(Sulfitobacter phage NYA-2014a), YP_001552271.1(Thalassomonas phage BA3),** YP_009030589.1(Pseudomonas phage KPP25), YP_009285843.1(Pseudomonas phage NP1), and YP_164304.1(Pseudomonas virus F116), respectively, and combining the bacteriophage strains with a suitable carrier or excipient.

21. A method for diagnosis of psoriasis comprising the steps of:

a) measuring the level of bacteria and bacteriophages in a sample from an area of a subject's skin to be tested;

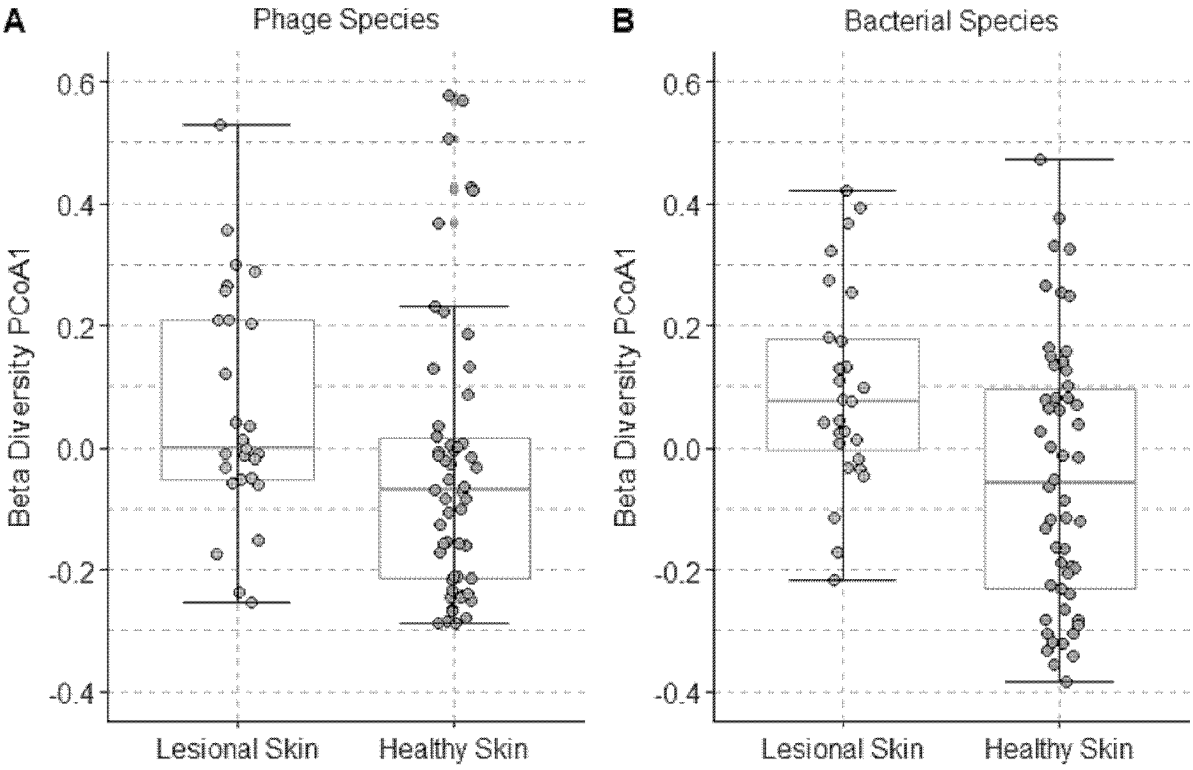
b) comparing the measurement obtained from step a) to a control; and

c) determining whether the individual has a risk of developing psoriasis, wherein a lower level of at least one of Acinetobacter phage Presley, Salmonella phage vB_SenS-Ent2, Bacillus phage SP-10, Pseudomonas phage O4, Haemophilus phage Aaphi23, Enterobacteria phage SfI, Bordetella virus BPP1, Mycobacterium phage DrDrey, Burkholderia virus BcepC6B, Rhodoferax phage P26218, Burkholderia virus phi1026b, Idiomarinaceae phage Phi1M2-2, Ralstonia phage RSK1, Sulfitobacter phage NYA-2014a, Thalassomonas phage BA3, Pseudomonas phage KPP25, Pseudomonas phage NP1, and Pseudomonas virus F116, as compared to a control and a higher level of Pseudomonas species, Acinetobacter and/or cutibacterum acnes as compared to a control indicates an increased risk of developing psoriasis.



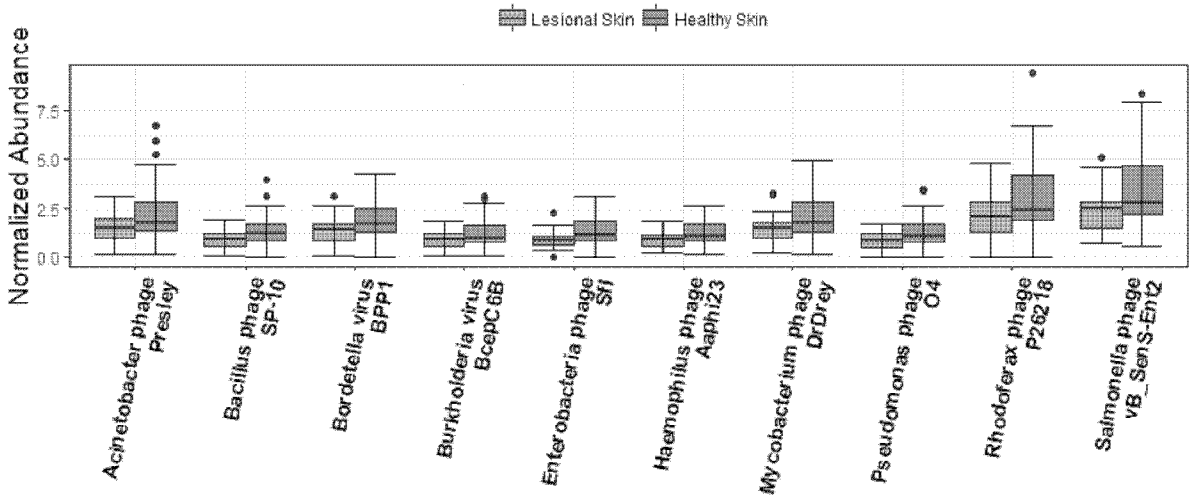
Stacked bar-plot shows the distribution of top 10 most abundant species and the rest of other species in microbial community. A, Composition of phage species across different groups of skin samples. B, Composition of bacterial species across different groups of skin samples. Letters E, F, K, and S indicate locations of skin samples (Elbow, Forearm, Knee and Scalp). The color of E, F, K and S indicates subtypes of skin samples (lesional skin in orange, contralateral non-lesional skin in lightblue, and family controls skin in lemonchiffon).

FIG. 1. Distribution of most abundant species in phage community and bacterial community across different samples.



Boxplots comparing the composition of microbial community between lesional skin and healthy skin through PCoA1 estimated beta diversity from Bray-Curtis distance. A, Difference of beta diversity PCoA1 between lesional skin and healthy skin for phage species community. Significantly difference of phage species beta diversity PCoA1 was found between two groups ($P < .05$). B, Difference of beta diversity PCoA1 between lesional skin and healthy skin for bacterial species community. Significant difference in bacterial species beta diversity PCoA1 was found between two groups ($P < .001$).

FIG. 2. Comparison of Beta Diversity PCoA1 for Phage and Bacterial Species community Between Lesional Skin and Healthy Skin.



Normalized abundance between lesional skin vs healthy skin for top ten most abundant phage species are shown in boxplots. The first quantile, median and the third quantile are marked by lines of boxes. In general, healthy skin had higher abundance of top ten most abundant phages than lesional skin.

FIG. 3. Abundance between lesional skin and healthy skin for top ten most abundant phage species

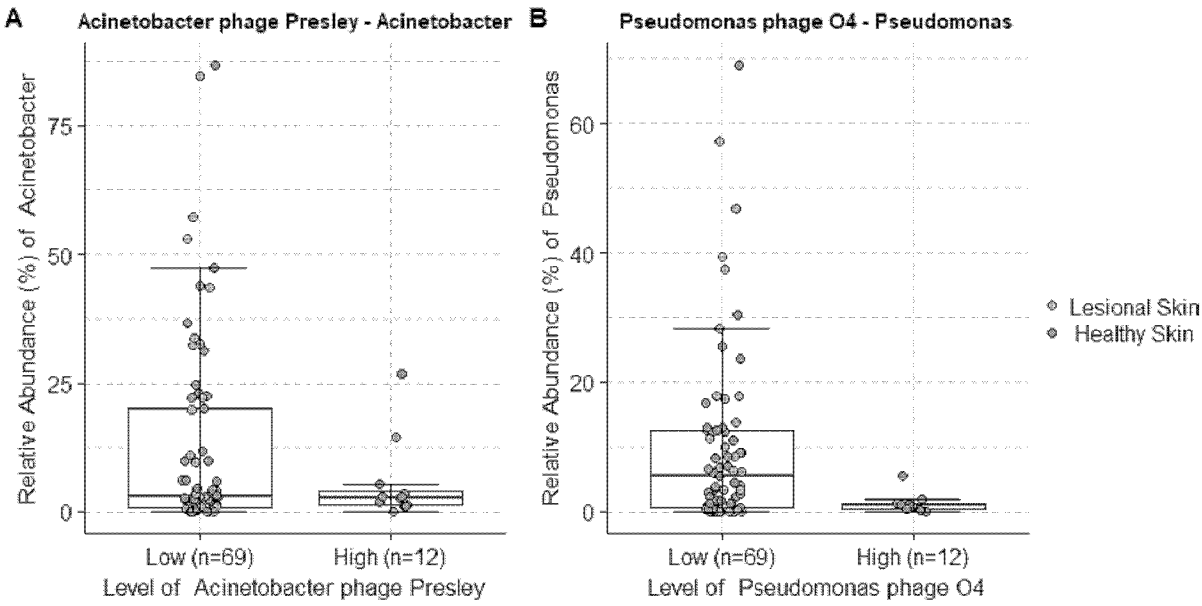


Figure 4 Boxplots of the host bacterial abundance between low phage level vs high phage level. In general, group with the high levels of phage abundance had lower host bacteria abundance. A, *Acinetobacter phage Presley - Acinetobacter*. B, *Pseudomonas phage O4 - Pseudomonas*. 25th percentile, Median, and 75th percentile of phage abundance were shown in boxes. The type of skin samples is indicated by color.

FIG. 4. Comparison of different levels of phage abundance to the host bacterial abundance

Phage Species	Median (Normalized Reads Count)	Q1(Normalized Reads Count)	Q3(Normalized Reads Count)	Rank
Salmonella phage vB_SenS-Ent2	2.58	1.88	4.00	1
Rhodoferax phage P26218	2.30	1.68	3.70	2
Mycobacterium phage DrDrey	1.67	1.15	2.40	3
Acinetobacter phage Presley	1.66	1.28	2.66	4
Bordetella virus BPP1	1.53	1.06	2.24	5
Bacillus phage SP-10	1.07	0.81	1.50	6
Burkholderia virus BcepC6B	1.02	0.77	1.54	7
Pseudomonas phage O4	1.00	0.72	1.54	8
Haemophilus phage Aaphi23	0.99	0.78	1.60	9
Enterobacteria phage SfI	0.98	0.75	1.53	10

Normalized reads count was calculated through reads count aligned to phage contigs divided by the lengths of contigs and total reads count for a sample and scaled in 1 million total reads per sample (RPKM).

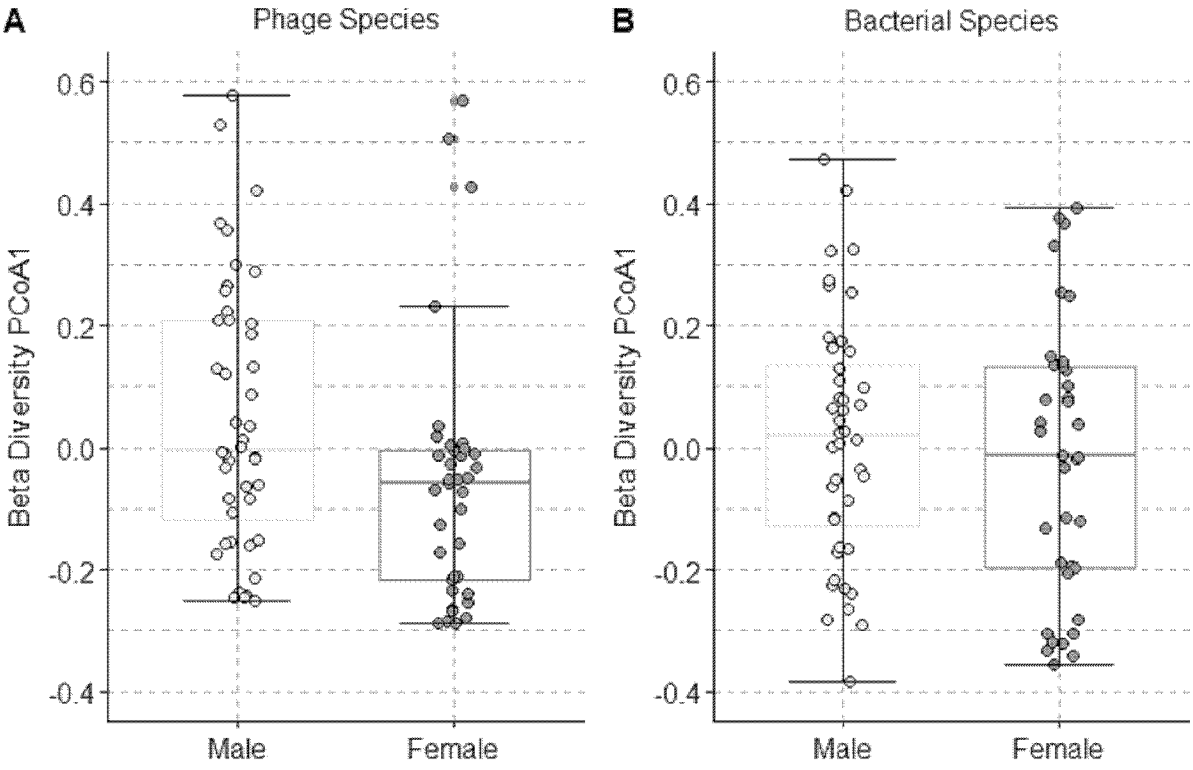
FIG. 5. Order of Top Ten Most Abundant Phage Species

Bacterial Species	Median (Relative Abundance (%))	Q1(Relative Abundance (%))	Q3(Relative Abundance (%))	Rank
Pseudomonas species	2.89	0.36	8.88	1
Acinetobacter species	2.26	0.51	5.91	2
Cutibacterium acnes	1.51	0.00	6.03	3
Moraxella osloensis	0.90	0.00	4.53	4
Campylobacter jejuni	0.48	0.21	1.64	5
Verrucomicrobia bacterium	0.44	0.00	1.05	6
Coxiella species	0.38	0.00	1.76	7
Mucilaginibacter paludis	0.29	0.00	0.69	8
Burkholderiales bacterium	0.28	0.00	0.64	9
Propionibacterium species	0.23	0.00	10.61	10

FIG. 6. Order of Top Ten Most Abundant Bacterial Species

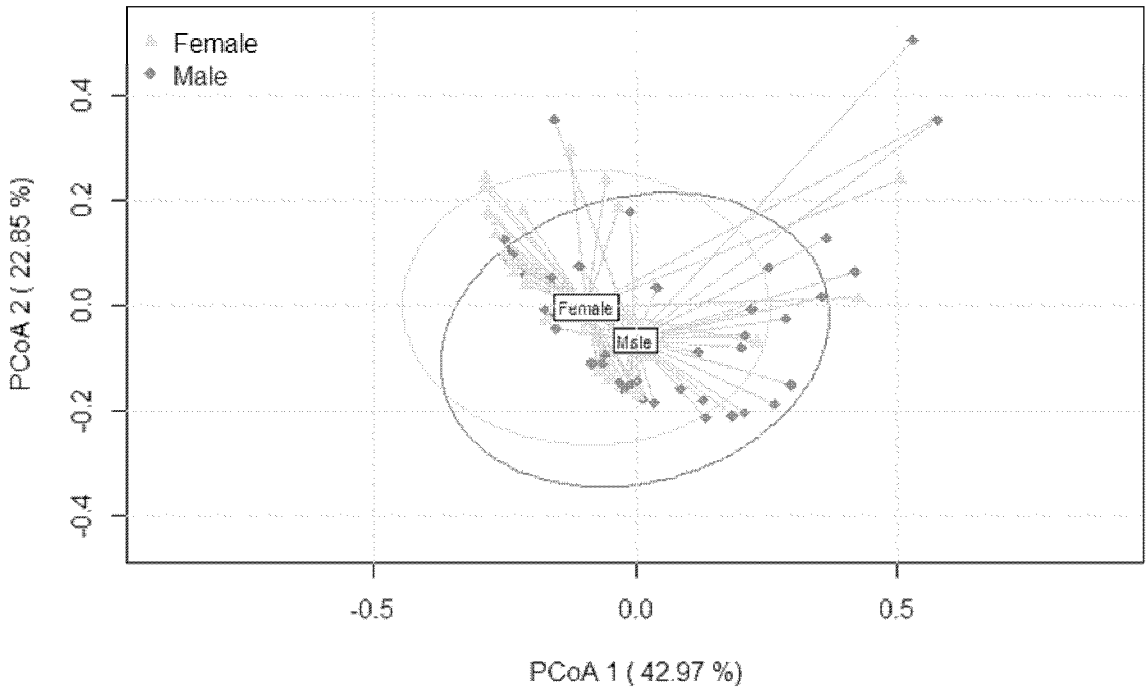
		Test of Differential Abundance for Lesional Skin vs Healthy Skin
	Rank in Abundance	Raw P (linear mixed model)
Acinetobacter phage Presley	4	0.009
Salmonella phage vB_SenS-Ent2	1	0.009
Bacillus phage SP-10	6	0.011
Pseudomonas phage O4	8	0.013
Haemophilus phage Aaphi23	9	0.014
Enterobacteria phage SfI	10	0.017
Bordetella virus BPP1	5	0.018
Mycobacterium phage DrDrey	3	0.022
Burkholderia virus BcepC6B	7	0.023
Rhodoferax phage P26218	2	0.027

FIG. 7. P values of Statistical Tests for Top Ten Most Abundant Phages



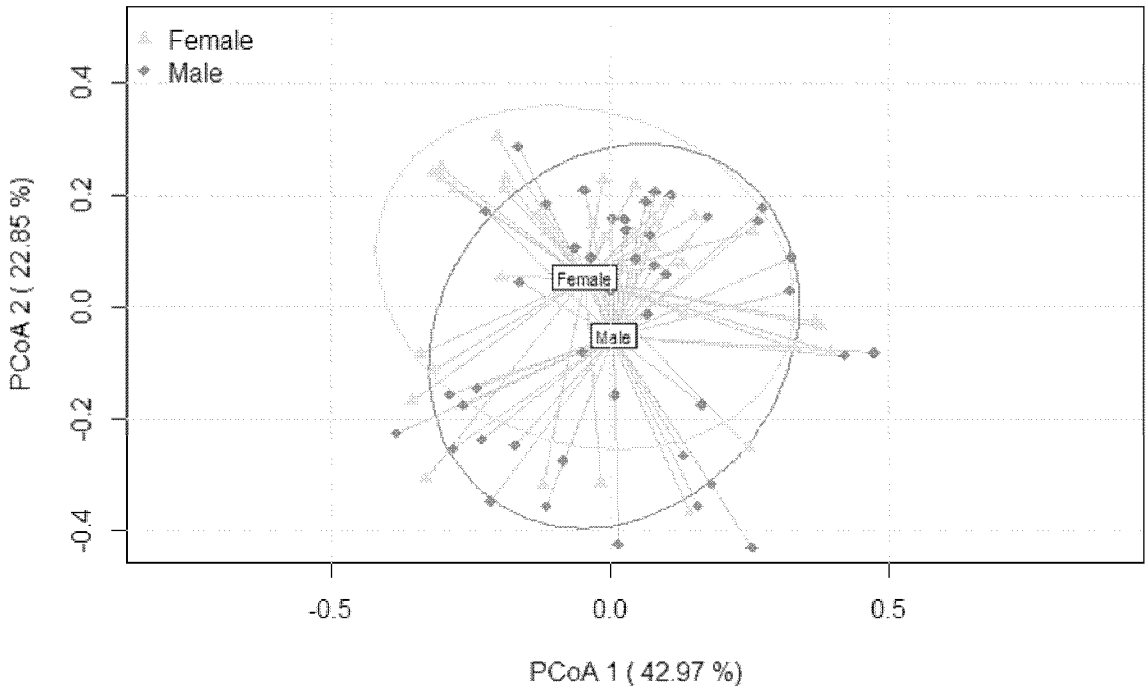
Boxplots compare the composition of microbial community between female and male through PCoA1 estimated beta diversity from Bray-Curtis distance. A, Difference of beta diversity PCoA1 between female and male for phage species community. Significantly difference of phage species beta diversity PCoA1 was found between two groups (P = .16). B, Difference of beta diversity PCoA1 between lesional skin and healthy skin for bacterial species community. Significantly difference of bacterial species beta diversity PCoA1 was found between two groups (P = .78).

FIG. 8. Comparison of Beta Diversity PCoA1 for Phage and Bacterial Species Community Between Two Groups of Sex



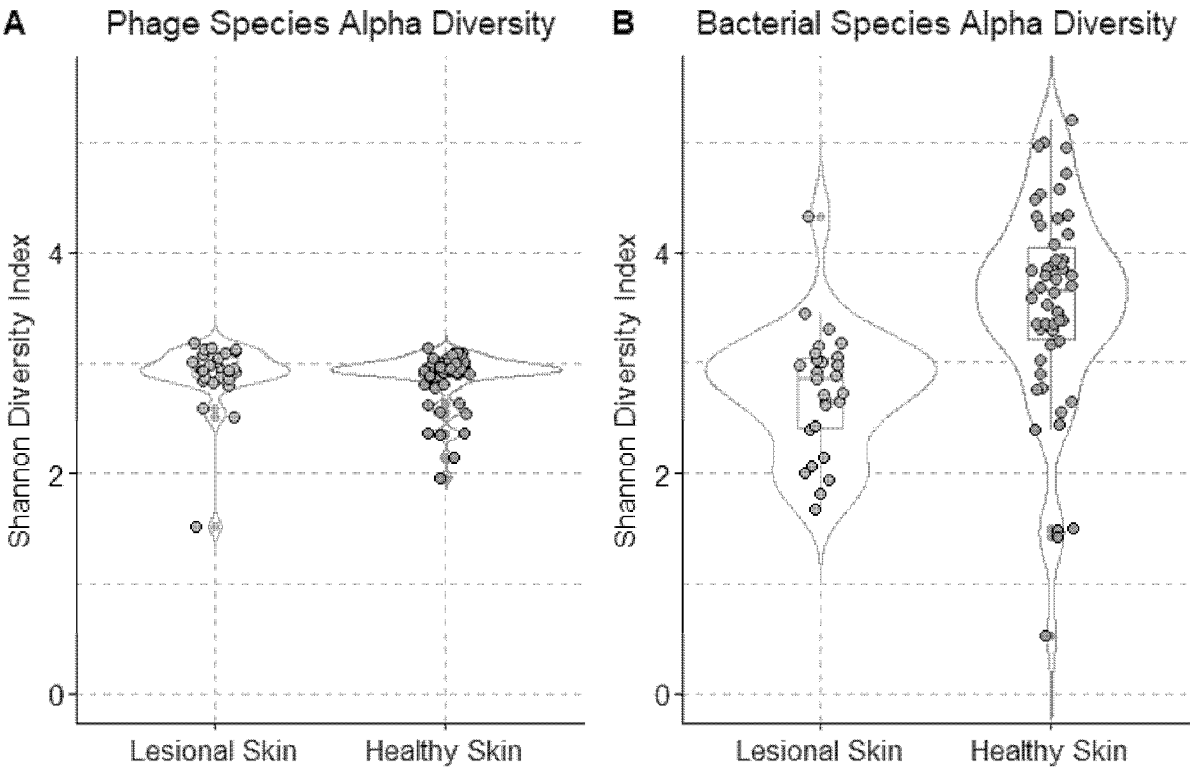
PCoA plot illustrates the differences of overall phage species composition (beta diversity) between female and male. The centroid of samples from each group is indicated with a text label inside of a square and connected to samples in the same group. Ellipses depict the 75% prediction areas of samples from each group.

FIG. 9A. PCoA Plot Illustrating Differences of Phage Species Composition Between Female and Male



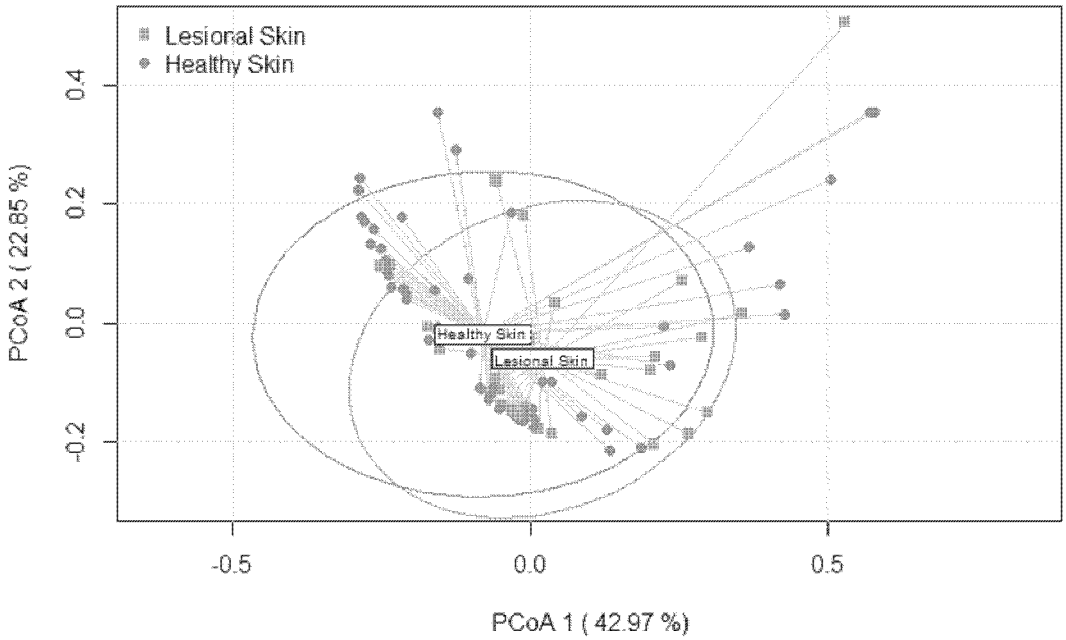
PCoA plot illustrates the differences of overall bacterial species composition (beta diversity) between female and male. The centroid of samples from each group is indicated with a text label inside of a square and connected to samples in the same group. Ellipses depict the 75% prediction areas of samples from each group.

FIG. 9B. PCoA Plot Illustrating Differences of Bacterial Species Composition Between Female and Male



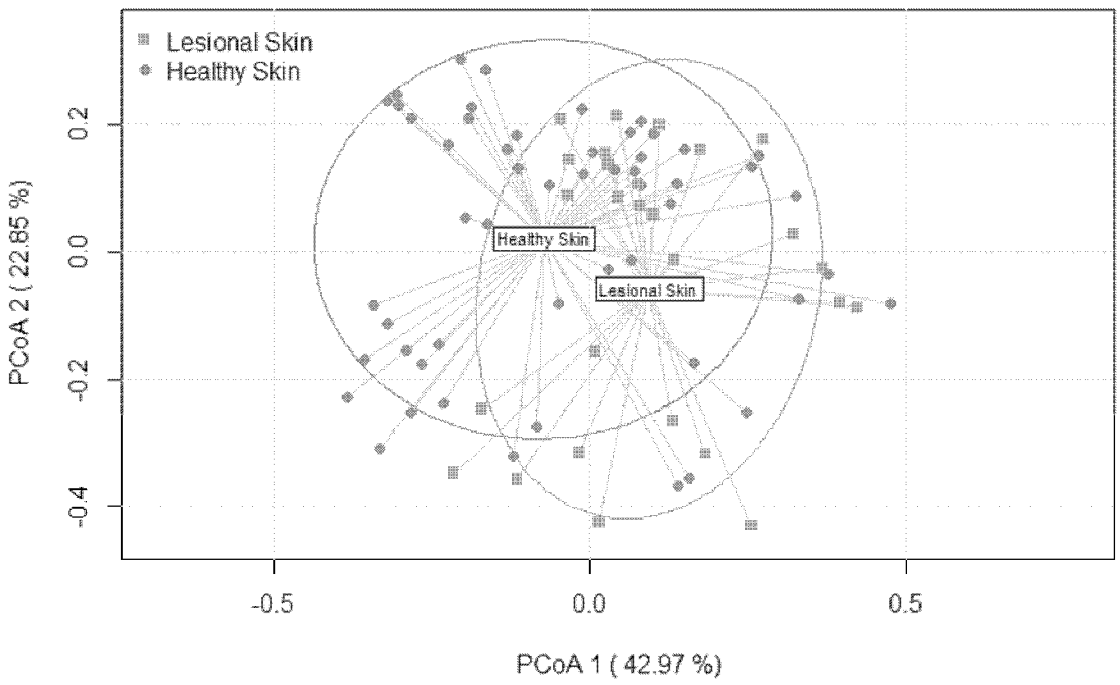
Comparison of alpha diversity measured by Shannon Diversity Index for different groups of skin samples (lesional skin vs healthy skin) is shown in violin plot with boxplot inside. Violin plot shapes the distribution of samples and boxplot indicates the median and IQR. A, Phage species alpha diversity has no difference between lesional skin and healthy skin ($P = .62$). B, Bacterial species alpha diversity in healthy skin is significantly higher than lesional skin ($P < .001$).

FIG. 10. Comparison of Alpha Diversity for Phage and Bacterial Species Between Lesional Skin and Healthy Skin



PCoA plot illustrates the differences of overall phage species composition (beta diversity) between lesional skin and healthy skin. The centroid of samples from each group is indicated with a text label inside of a square and connected to samples in the same group. Ellipses depict the 75% prediction areas of samples from each group.

FIG. 11A. PCoA Plot Illustrating Differences of Phage Species Composition Between Lesional Skin and Healthy Skin

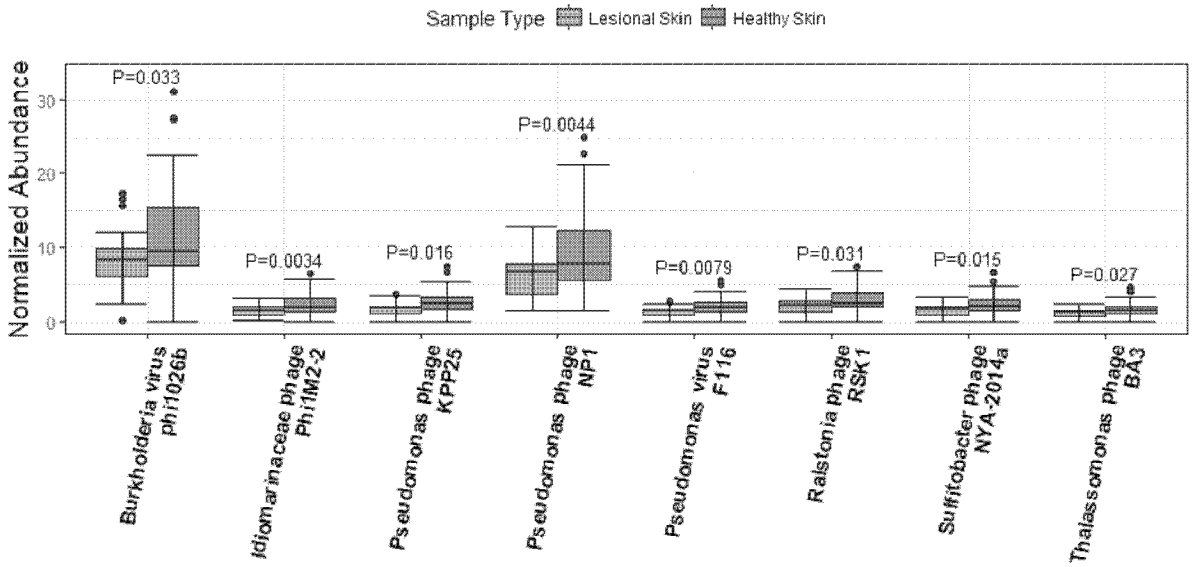


PCoA plot illustrates the differences of overall bacterial species composition (beta diversity) between lesional skin and healthy skin. The centroid of samples from each group is indicated with a text label inside of a square and connected to samples in the same group. Ellipses depict the 75% prediction areas of samples from each group.

FIG. 11B. PCoA Plot Illustrating Differences of Bacterial Species Composition Between Lesional Skin and Healthy Skin

Phage Species	Median (Normalized Read Count)	Q1(Normalized Read Count)	Q3(Normalized Read Count)	Rank
Burkholderia virus phi1026b	8.99	6.80	13.90	1
Pseudomonas phage NP1	7.20	5.28	10.82	2
Burkholderia virus phi6442	5.43	0.43	8.78	3
Pseudomonas phage phiPSA1	4.31	0.14	6.29	4
Ralstonia phage RSK1	2.41	1.84	3.46	5
Pseudomonas phage KPP25	2.03	1.53	3.14	6
Sulfitobacter phage NYA-2014a	1.79	1.31	2.73	7
Idiomarinaceae phage Phi1M2-2	1.79	1.15	2.77	8
Pseudomonas virus F116	1.53	1.22	2.45	9
Thalassomonas phage BA3	1.40	1.03	1.99	10

FIG. 12. Order of Top Ten Most Abundant Category Two Phage Species



Eight species over the top ten dominate *category two* phage species had differential abundance between lesional skin and healthy skin and are shown in boxplots. The first quantile, median and the third quantile are marked by lines of boxes. P values from the linear mixed effects model are marked above the boxplots.

FIG. 13. Differential abundance between lesional skin and healthy skin for dominate *category two* phage species

Phages	**% Level**
Acinetobacter phage Presley	4.19
Pseudomonas phage O4	2.25
Pseudomonas phage NP1	16.50
Pseudomonas virus F116	3.52
Pseudomonas phage KPP25	4.63

% Level of each was estimated by the relative percentage of each species over 20 dominate phage species (top 10 *category one* phage species and top 10 *category two* phage species)

FIG. 14. Suggested minimum starting % level of Potential Probiotics Phage Species

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/110309

A. CLASSIFICATION OF SUBJECT MATTER

C12N 7/00(2006.01)i; C12N 7/01(2006.01)i; C12Q 1/70(2006.01)i; A61K 35/76(2015.01)i

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)

C12N,C12Q,A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS, VEN, CNKI, ISI web of Knowledge, GOOGLE, BAIDU, Patentics,Bio-Sequence Database of Chinese Patent, NCBI, EBI: all bacteriophage strains involed in claim 1 such as Acinetobacter phage Presley,all NCBI accession Nos involved in claim 1 such as YP_009007647.1, bacteriophage,antibiotics, psoriasis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PESLYAK, M.Y. "Model of pathogenesis of psoriasis" *MYPE*, 14 April 2012 (2012-04-14), page 1-84	1-21
Y	PESLYAK, M.Y. "Model of pathogenesis of psoriasis" *MYPE*, 14 April 2012 (2012-04-14), page 1-84	7-21
X	"YP_009007647.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_009007647.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_009009926.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2019	**10 January 2020**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **SU,Baowei** Telephone No. **86-(10)-53961933**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"YP_009009926.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_007003398.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_007003398.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_009304497.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_009304497.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"NP_852738.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"NP_852738.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_009147451.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_009147451.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"NP_958679.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"NP_958679.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_008409492.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_008409492.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_024932.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_024932.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_009222582.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"YP_009222582.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"NP_945032.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"NP_945032.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_009104301.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_009104301.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_008853829.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_008853829.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_009146206.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_009146206.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_001552271.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_001552271.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_009030589.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_009030589.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_009285843.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6
Y	"YP_009285843.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	7-21
X	"YP_164304.1" *GENBANK*, 13 August 2018 (2018-08-13), the whole document	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/110309

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"YP_164304.1" *GENBANK,* 13 August 2018 (2018-08-13), the whole document	7-21
X	"30Jun2018_phages.complete_genomes_accession" *MILLARDLAB,* 30 June 2018 (2018-06-30), the whole document	1-6
Y	"30Jun2018_phages.complete_genomes_accession" *MILLARDLAB,* 30 June 2018 (2018-06-30), the whole document	7-21
X	WO 2010062837 A2 (THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTE) 03 June 2010 (2010-06-03) claims 1-49, pages 14-15、22 of description	1-6
Y	WO 2010062837 A2 (THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTE) 03 June 2010 (2010-06-03) claims 1-49, pages 14-15、22 of description	7-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/110309

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **10-19**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 10-15 are directed to a method of treating or preventing psoriasis in a subject comprising to administering to the subject a therapeutically effective amount of the pharmaceutical composition according to any one of claims 1-6. Claims 16,18-19 are directed to a method of cosmetic treatment comprising a step of applying on a subject the dermatological composition of claim 8. Claims 17-19 are directed to a method for improving condition of a subject's skin by modifying the microbiome in the subject comprising the step of contacting the subject's skin with the composition of claim 8.

[2] The subject matter of claims 10-19 relate to methods of treatment for diseases, and therefore does not warrant an international search according to the criteria set out in Rule 39.1(iv). However, the search has been carried out and based on pharmaceutical composition according to any one of claims 1-6 in the manufacture of a medicament (claim10-15) , cosmetic (claims 16,18-19) or dermatological composition(claim17-19) for treating psoriasis in a human subject.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/110309

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2010062837 A2	03 June 2010	WO 2010062837 A3	23 September 2010
		US 2012020994 A1	26 January 2012