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(54) Title: METHODS FOR PROMOTING WOUND HEALING

(57) Abstract: The invention relates to methods for the promotion of wound healing. Specifically, methods for treating patients having wounds comprising administering the immunomodulator, Product R, are disclosed. Pharmaceutical compositions and kits comprising Product R, an additional medicament, and pharmaceutically acceptable carriers are also disclosed. The disclosed methods are useful for promoting wound healing for a wide variety of wounds, ulcers and burns.



WO 2006/026604 A2

METHODS FOR PROMOTING WOUND HEALING

1. FIELD OF THE INVENTION

5 [0001] The present invention relates to methods for using Product R, a peptide-nucleic acid composition, to promote wound healing and/or treat loss of appetite or fatigue in patients suffering from a wound. The methods are applicable for treating a wide variety of wounds, including ulcers and burn injuries.

2. BACKGROUND OF THE INVENTION

10 2.1. Wounds and Wound healing

[0002] Wound healing is the process through which the repair of damaged tissue(s) is accomplished. Wounds can range from minor abrasions to complicated life-threatening deep lacerations. Wounds can be classified in general into two main classes: 1) acute wounds, such as those acquired through trauma, surgical wounds, burn injuries or the
15 wounds to donor sites for autologous skin grafts; and 2) chronic wounds, such as venous homeostasis ulcers, diabetic ulcers and decubitus ulcers, which are of long duration and progressive.

[0003] The evolution of the wound healing process is described in three main phases: 1) The inflammatory or cleansing stage; 2) the proliferative or granulation phase;
20 and 3) the maturation and remodeling or epithelialization phase. The inflammatory stage occurs during the first few days after trauma. The wounded area begins its attempts to restore its normal state by constricting blood vessels to control bleeding. Platelets and thromboplastin are formed in the wound to produce clots. An inflammatory reaction with the influx of polymorphonuclear leukocytes to begin cleaning the wound of dead tissue and
25 contaminating organisms occurs. The inflammatory process serves mainly to cleanse the wound. Too much inflammation interferes with the process of wound healing.

[0004] After the inflammatory phase, the proliferative stage of wound healing can last about three weeks or longer. Fibroblasts produce collagen to begin the granulation process in the wound. The wound gradually contracts, blood vessels are formed to nourish
30 new tissue and a covering epithelial layer is formed.

[0005] The maturation and remodeling stage may last up to two years (even up to five years for the healing of burns). The formation of new collagen changes the shape of the wound and increases the strength of the scar that forms; however, scar tissue is at best 80% as strong as the original tissue.

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[0006] Polymorphonuclear leukocytes (PMNs) are the first cells to appear in the wound within the first 24 hours. Macrophages enter the wound about 48 hours after injury with peak numbers achieved about the third day after injury. The macrophages are derived from circulating monocytes by a combination of migration and chemotaxis. The
5 macrophages are longer lived in the wound and linger in the wound until healing occurs. T-lymphocytes appear about the fifth day after injury. The presence and activation of macrophages and T-lymphocytes are critical to the normal process of wound healing.

[0007] Cytokines and chemokines play important roles in the process of wound healing. Burn wounds are also marked by a production of endogenous cytokines (Stallo et al., 2003, *Burns* 29:641-647). Among the cytokines and chemokines important in wound
10 healing, interleukin-1- beta (IL-1beta) is important for chemotaxis during the inflammation phase and may also play a role in collagen synthesis (Castagnoli et al., 2002, *Wound Repair Regen.* 10:107-108). Tumor necrosis factor-alpha (TNF-alpha) stimulates angiogenesis and is also involved in chemotaxis. Interferon-gamma (IFN-gamma) appears to play a role
15 during the proliferative phase. Interleukin-1 beta induces fever, adrenocorticotrophic hormone (ACTH) release, enhances the synthesis of TNF-alpha and IFN-gamma and activates PMNs. Interleukin-2 activates macrophages, T-cells and NK-cells. Interleukin-6 induces fever and enhances the release of acute phase reactants from the liver. Interleukin-8, an important pro-inflammatory chemokine, enhances neutrophil adherence, chemotaxis
20 and granule release.

[0008] Immunomodulators have been shown to promote wound healing. For example, alpha thymosin, a T cell stimulator, has shown positive activity in wound healing (Malinda et al., 1998, *J. Immunol.* 160:1001-1006).

[0009] While minor wounds generally heal completely on their own in a healthy
25 patient, more severe wound injuries do not heal completely, resulting in scar tissue and/or other complications or do not heal at all. Lacerations, however, tend to become more inflamed than clean surgical wounds, including wounds resulting from surgical amputations, and are more difficult to heal. At a simple level this may be due to the trauma of the laceration that results in dead tissue and contamination with bacteria, requiring a
30 greater inflammatory response to cleanse the wound. Furthermore, vascular perfusion of traumatized tissue may be compromised by damage to both large and small blood vessels and lymphatic channels.

[0010] The natural healing of wounds is complicated by many factors which can adversely affect the wound healing process, including the presence of necrotic debris,
35 foreign material, infection, medication, and the age, health, and nutritional status of the

~~injured individual. In addition, any process that impedes peripheral blood circulation, such as arteriosclerosis, prolonged pressure, varicose vein disease, and venous stasis, can adversely affect the delivery of oxygen, nutrients, chemical signals, and appropriate cell types to mediate healing in an injured patient, will impair wound healing. Certain partial~~
5 and full thickness injuries, such as burns, skin grafts, and various types of ulcers, resist repair and produce significant pain and discomfort for the afflicted individual.

[0011] Bacterial wound infection is the most common local cause for prolonged wound healing. Human skin is typically colonized by a number of microorganisms, including *Candida albicans*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and some
10 *Streptococcus* strains. Thus, any wound which exposes underlying tissues to the environment becomes infected with at least resident microbial flora. Wounds which are well tended and in highly vascularized tissue resist infection, while those in ischemic tissue are much more susceptible to infection.

[0012] Medications used to treat disorders can produce impaired wound healing.
15 Chemotherapy, used to eliminate dividing cells in cancer patients, also suppresses the ability of such a patient to heal wounds, which is also dependent upon new cell growth. Steroids negatively impact all three phases of wound repair, inhibiting the initial inflammatory response, slowing the production of new epithelium and vascular tissue, and weakening the collagen matrix in the scar tissue (Bryant, 1987, *J. Enterostomal Therapy*,
20 14: 262-66).

[0013] The physical condition of the patient is also important in wound healing. As age increases, the ability to repair injured tissue decreases, as the skin becomes thinner and the number of fibroblasts and amount of total skin collagen decrease (Shuster et al., 1975, *Br. J. Dermatol.* 93: 639-43). Disease states such as alcoholism, anemia, diabetes,
25 malnutrition, shock, and uremia lead to impaired oxygen and nutrient delivery to the wound site, thereby inhibiting the healing process. Also, diseases leading to monocytopenia can significantly impair wound healing.

[0014] The severe nature of certain wounds and factors which affect the wound healing process indicate the need for improved agents for promoting wound healing. In
30 particular, there is a need for a non-toxic agent that effects the following: 1) Keep the wound clean and minimize the development of necrotic tissue; 2) Build a healthy tissue base for the wound (granulation tissue), allowing the influx of white blood cells and the action of wound healing promoting molecules, including growth factors and relevant cytokines and chemokines; 3) Prevent infection of the wound and allow the wound to heal

by primary intention with suture closure; 4) Decrease scar formation and promote natural epithelialization; and 5) Decrease the time required for wound healing.

2.2. Product R

[0015] Reticulose[®] emerged as an antiviral product in the 1930's. While it was
5 originally believed to be a product composed of peptone, peptides and nucleic acids, the precise composition remains unidentified. A method for preparing Reticulose[®] is provided in U.S. Patent No. 5,849,196, herein incorporated by reference in its entirety. Nevertheless, Reticulose[®] has demonstrated an ability to inhibit rapidly the course of several viral diseases. It is nontoxic, miscible with tissue fluids and blood sera and free from
10 anaphylactogenic properties.

[0016] As taught by U.S. Patent No. 5,849,196, the components present in the conventional composition of Reticulose[®] that are greater than 15 kDa in molecular weight are more effective in treating viral diseases such as HIV, influenza virus, herpes simplex virus, etc., while the components having a molecular weight in a range of approximately 1
15 to 15 KDa function as phagocytosis inhibitors.

[0017] Reticulose[®] suffers from several disadvantages: 1) the method of preparation does not ensure that each preparation produces the finished components in the same ratio, i.e., the final product is not reproducible; 2) the conventional method of preparation produces a wide range of the finished components, which makes the quality control of the
20 preparation extremely difficult, if possible, because too many parameters need to be determined; 3) the presence of the higher molecular weight components, such as 25 KDa component, essentially peptides, increases the risk of hypersensitivity or immune reaction and renders the product less stable. Therefore, it is desirable to have a product devoid of the deficiencies of conventional Reticulose[®] while maintaining its therapeutic properties.

[0018] U.S. Patent Nos. 6,303,153 and 6,528,098, both of which are herein
25 incorporated by reference in their entireties, disclose the preparation of Product R, a composition derived from the same starting materials as used in preparing Reticulose[®], but distinct from Reticulose[®]. For example, material greater than 14 kDa molecular weight is removed when preparing Product R.

[0019] Product R is an immunomodulator with a favorable safety profile affecting
30 the production of pro-inflammatory chemokines and cytokines, driving the immune response towards a normal state. In particular, Product R modulates the expression of chemokines and cytokines. Product R stimulates macrophages to produce pro-inflammatory cytokines and chemokines, including MCP-1, IL-8 and IL-6 (Lazzarino *et al.*,
35 2001, *Cytokine*, 14:234-239; Lazzarino *et al.*, 2000, *Immunol. Lett.* 74:189-195). On the

other hand, in highly activated macrophages, Product R inhibits the synthesis of these pro-inflammatory chemokines. Product R may also increase levels of IL-2R. IL-2R can stimulate populations of both T and B cells.

[0020] Insofar as the applicant knows, Product R has never been used, nor suggested for promoting wound healing. It is now discovered that Product R can be used for the promotion of wound healing.

[0021] Although considerable advances have occurred in the field of wound healing, the healing of wounds still presents a formidable challenge to the physician. This is particularly true in diabetic patients, those with impaired circulation in the skin, the elderly, and those who are prone to infection, such as immunocompromised patients. When wounds do heal, they frequently do so with cosmetic disfigurement such as scarring or discoloration. The increase in cosmetic plastic surgery has also resulted in increased incidences of surgical wounds that scar upon healing. Thus, there is a clear need for improved methods of wound healing comprising administering compositions such as Product R that are non-toxic, well-tolerated and that can be used concomitantly with other medications.

3. SUMMARY OF THE INVENTION

[0022] The present invention provides methods for promoting wound healing in a patient, comprising administering to said patient an amount of Product R effective to promote wound healing. The present invention also provides methods for treating loss of appetite and fatigue in a patient, preferably a patient suffering from a wound or burn injury, comprising administering to said patient an amount of Product R effective to treat loss of appetite and fatigue. In the methods and compositions of the invention, Product R comprises nucleotides and peptides have molecular weights not more than 14 KDa and substantially not more than 8 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4 ($\pm 10\%$) at 260 nm/230 nm. In a preferred embodiment, the patient is a human. In certain embodiments, the amount of Product R effective to promote wound healing and/or treat loss of appetite and fatigue is in a range from about 0.5 microliters to about 100 microliters per kilogram of body weight per day, or from about 2.5 microliters to about 40 microliters per kilogram of body weight per day, or from about 10 microliters to about 25 microliters per kilogram of body weight per day. In certain embodiments of the invention, Product R is administered parenterally, topically or systemically. In another embodiment,

Product R is administered topically to a wound in a dose adequate to encompass the total area of the wound.

[0023] The methods of the invention can be employed to promote wound healing in a wide variety of wounds. In certain embodiments, the wound is a result of decubitus ulcers, diabetic ulcers, surgical wounds or burn injury.

[0024] The present invention also encompasses methods for promoting wound healing in a patient, comprising administering to said patient an amount of Product R effective to promote wound healing and an effective amount of another medicament. The present invention also encompasses methods for treating loss of appetite or fatigue in a patient, preferably a patient suffering from a wound or burn injury, comprising administering to said patient an amount of Product R effective to promote wound healing and an effective amount of another medicament. In certain embodiments, the other medicament is an antibiotic, a biological response modifier, *e.g.*, a cytokine, or a wound healing factor.

[0025] The present invention also comprises pharmaceutical compositions and kits comprising 1) an amount of Product R effective to promote wound healing; 2) a biological response modifier or a wound healing factor agent; and 3) a pharmaceutically acceptable carrier.

[0026] Antibiotics useful in the methods of the invention include, but are not limited to, penicillin, cephalosporin, griseofulvin, bacitracin, polymyxin B, amphotericin B, erythromycin, neomycin, streptomycin, tetracycline, vancomycin, gentamicin, and rifamycin. Biological response modifiers useful in the methods and compositions of the invention include, but are not limited to, interferon- α , interferon- γ , interleukin-2, interleukin-4, interleukin-6, and tumor necrosis factor. Wound healing factors useful in the methods and compositions of the invention include, but are not limited to, interferon (IFN)- β , IFN- γ , interleukin (IL)-1, IL-2, IL-4, IL-5, IL-15, tumor necrosis factor, flt-1 ligand, arginine, connective tissue growth factor, adenosine, cyclic adenosine monophosphate, the fibroblast growth factor family, tumor growth factor- α , tumor growth factor- β (1 and 2), vascular endothelial growth factor, the epidermal growth factor family, the platelet derived growth factor family, the insulin-like growth factor family, nitric oxide, macrophage-stimulating protein, and macrophage-derived growth factor.

4. DETAILED DESCRIPTION OF THE INVENTION

[0027] The inventors have discovered that Product R can promote the wound healing process, particularly when administered topically, *i.e.*, to the surface of the wound site, or systemically. The present invention provides methods and compositions for

promoting wound healing with Product R. Product R so delivered can be used for all wound types, acute or chronic, such that the wound undergoes healing more rapidly than similar wounds left to heal naturally or which are treated with currently available methods. Without being bound by any theory, Product R is believed to modulate the immune system to promote wound healing.

[0028] Product R (AVR118; Advanced Viral Research Corp., Yonkers, NY) is a composition comprising the breakdown products of casein, peptone, RNA, and serum albumin. The manufacturing process, composition, and the chemical and physical and some biological properties of Product R are described in U.S. Patent Nos. 6,303,153 and 6,528,098, both of which are herein incorporated by reference in their entireties.

[0029] Product R has been used as a synonym of Reticulose[®] in some literature. For the purpose of the present application, Product R and Reticulose[®] represent two distinct products.

[0030] Product R is a therapeutic composition for treating viral infections and stimulating the immune system comprising nucleotides and peptides have molecular weights not more than 14 KDa and substantially not more than 8 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4 ($\pm 10\%$) at 260 nm/230 nm.

[0031] Generally, Product R is prepared according to the following manner.

[0032] First, the starting materials casein, beef peptone, RNA, bovine serum albumin (BSA), and sodium hydroxide are suspended in proportions of, by weight, 35-50% (casein), 15-40% (beef peptone), 10-25% (RNA), 1-10% (BSA) and 5-25% (sodium hydroxide) in an appropriate volume of distilled water. All starting materials are generally available or otherwise can be readily prepared by a person of ordinary skill in the art. While any RNA is suitable for the intended purpose of the present invention, plant RNA is preferred and yeast RNA is the most preferred. The ratio of total proteins versus the volume of distilled water is generally about 1.5-2.5 to about 100 by weight, preferably about 2.2 to about 100 by weight. This means that every 1.5-2.5 grams of the total proteins are suspended in about 100 milliliters of distilled water.

[0033] The suspension as prepared above is then autoclaved at a pressure of approximately 5-15 lbs., preferably 8-10 lbs. under an elevated temperature in a range, for example, from about 65°-150 °C, preferably from about 90° -110 °C, over a period of approximately 2-10 hours, preferably more than 3 hours. As known to a person of ordinary skill in the art, under such conditions RNA may be completely hydrolyzed into nucleotides.

~~After autoclaving, the solution is cooled down to room temperature, and then allowed to stay at a temperature of 3° to 8 °C for at least 12 hours to precipitate insoluble elements.~~

Alternatively, the cooled solution may be centrifuged at a temperature below 8 °C to remove the precipitates.

5 [0034] The resulting solution is then filtered through a 2 micron and a 0.45 micron filters under an inert gas such as nitrogen or argon at a pressure of about 1-6 psi. In a similar manner the solution is filtered again through a pyrogen retention filter, preferably 0.2 micron.

[0035] After the above filtration, the solution may be cooled at 3 to 8 °C again for at least about 12 hours and filtered again in the same way as described above.

10 [0036] The resulting filtrate is then assayed for total nitrogen content using methods known to a person of ordinary skill in the art such as Kjeldahl method (Kjeldahl, Z. 1983, Anal. Chem., Vol. 22:366), and its improvements. Based on the assay, the filtrate is then diluted with chilled distilled water to an appropriate volume having a preferred total
15 nitrogen content ranging from 165 to 210 mg/ml.

[0037] The pH of the diluted solution is then adjusted with HCl to a physiologically acceptable pH, preferably to about 7.3 to 7.6, after which the diluted solution is filtered again through a 0.2 micron filter under an inert gas as described above.

20 [0038] Product R so produced contains essentially nucleotides, nucleosides and free nucleic acid bases of low molecular weights from a complete hydrolysis of RNA and small peptides from partial hydrolysis of the proteins. It is possible that the base hydrolysis of the proteins also produces free amino acids.

[0039] It is understood that the use of a filtration technique is essentially to remove bacteria or other particles having similar size to or larger size than bacteria. Thus, any filter
25 regardless of its manufacturer or material from which it is made is suitable for the intended purpose. All filters used in the present process are widely available to a person of ordinary skill in the art.

[0040] The final filtrate is then filled and sealed into appropriate vials, such as 2 ml or 10 ml glass vials under an inert gas. The filled vials are autoclaved for final sterilization,
30 after which they are ready for use.

[0041] An analysis of the composition of Product R reveals that Product R contains two major components, which are exhibited as two bands having molecular weights of 5.2 kDa and 4.3 kDa on a SDS-polyacrymide gel electrophoresis, namely peptide-A and peptide-B, respectively. Peptide-A is a 31 amino acid long peptide of 5.2 KDa molecular
35 weight derived from bovine casein. It is a straight chain peptide lacking any cysteine-

cysteine cross links. The structure is remarkable for six proline residues spaced throughout the molecule and four basic glutamine residues. Since proline residues can induce bends in peptide chains, the structure is likely a highly folded peptide. Peptide-B comprises a 21 amino acid long linear peptide of 4.3 KDa molecular weight covalently linked at the hydroxyl group of a serine residue at position 18 to a diadenosine dinucleotide unit through a diphosphodiester linkage at the 3'-position. Peptide-A and peptide-B are present in the Product R composition in an approximately equal amount and the total amount of these two peptides is about 4.8-5.3 mg/ml, determined by a Lowry protein assay.

[0042] The sequence of peptide A is:

10 KVLVPVQKAVPYPQRDMPIQAFLLYQEPVLG (SEQ ID NO. 1). The sequence of peptide B is: GEIPDAGGRIVDYYVGFSDSV (SEQ ID NO. 2). Product R also comprises nucleosides, nucleoside diphosphates and nucleoside monophosphates. There are sixteen identified constituent compounds present in the Product R formulation - 3 nucleosides, two nucleoside diphosphates and eight nucleoside monophosphates, together with two peptides (one of them a peptide-nucleic acid conjugate) and sodium chloride.

15 [0043] The physical, chemical and biological properties of Product R are further described in U.S. Patent Nos. 6,303,153 and 6,528,098, the contents of which are incorporated by reference in their entireties.

4.1. Target Wounds and Wound-related Conditions

20 [0044] The methods of the present invention are applicable for treating any type of wound to promote wound healing. The methods of the present invention are also applicable for treating conditions, such as loss of appetite and fatigue, in a patient, preferably a patient suffering from a wound or burn injury. Certain wounds heal normally without therapeutic intervention. In these cases, the methods of the invention can quicken the healing process. However, there are numerous disorders in which wound healing plays a role, such as, for example, diabetes mellitus, arterial occlusive diseases, psoriasis, Crohn's disease, epidermolysis bullosa, age-related skin changes or innervation disorders. Wound healing disorders lead to a delayed healing of wounds or to chronic wounds. These disorders can be caused by the nature of the wound (*e.g.* large-area wounds, deep and mechanically expanded operation wounds, burns, trauma, decubitus), medicinal treatment of the patients (*e.g.* with corticoids) but also by the nature of the disorder itself. For example, 25% of the patients with Type II diabetes thus frequently suffer from chronic ulcers ("diabetic foot"), of which approximately half necessitate expensive hospitalized treatments and nevertheless finally heal poorly. Diabetic foot causes more stays in hospital than any other complication associated with diabetes. The number of these cases in diabetes Type I and II is on the

increase and represents 2.5% of all hospital admissions. Moreover, wounds heal more poorly with increasing age of the patients. An acceleration of the natural wound healing process is often desirable as well in order to decrease, for example, the danger of bacterial infections or the rest periods of the patients.

- 5 [0045] Clinically, wounds are divided into three categories (Clinical Guide to Wound Care, Hess, Ed., Lippincott Williams & Wilkins; 4th edition (2002)). These categories and representative examples are provided below.

[0046] Wounds

- [0047] Acute wound: a wound caused by trauma or surgery; usually requiring
10 limited local care.

[0048] Chronic wound: a wound which takes longer than usual to heal because of underlying conditions, such as pressure, diabetes mellitus, poor circulation, poor nutritional state, immunodeficiencies, or infection.

- [0049] Full-thickness wound: tissue destruction extending through the second layer
15 of skin (dermis) to involve subcutaneous tissue and possibly muscle or bone.

[0050] Laceration: a torn or jagged wound.

[0051] Partial-thickness wound: tissue destruction through the first layer of skin (epidermis), extending into, but not through, the dermis.

[0052] Ulcers

- 20 [0053] Arterial ulcer: an ulcer caused by poor blood supply; related to the presence of arterial occlusive disease; symptoms include pain and tissue loss.

[0054] Diabetic ulcer: an ulcer caused by trauma or pressure secondary to neuropathy or vascular disease related to diabetes mellitus.

- [0055] Pressure ulcer (decubitus ulcer): an ulcer caused by poor blood supply from
25 pressure, also called a bedsore or pressure sore.

[0056] Venous ulcer: local losses of epidermis and various levels of dermis and subcutaneous tissue, occurring over or near the malleoli of the distal lower extremities; caused by edema and other sequelae of impaired venous return.

[0057] Burns

- 30 [0058] Superficial (first-degree burn): damage limited to the epidermis characterized by erythema, hyperemia, tenderness, and pain.

[0059] Partial-thickness (second-degree burn): superficial to deep partial-thickness wound characterized by large blisters, edema, pain, and wet, weeping, and shiny surface.

[0060] ~~PCT/US2005/030798~~ Full-thickness (third-degree burn): full-thickness wound characterized by deep-red, black, or white appearance; edema; painless nerve ending damage; and exposed subcutaneous fat layer.

4.2. Dosage and Administration

5 [0061] The individual, patient or subject in whom promotion of wound healing, or treatment of loss of appetite or fatigue, is desired is an animal, preferably a mammal, a non-human animal or primate, and most preferably human. The term "animal" as used herein includes, but is not limited to, companion animals, such as cats and dogs; zoo animals; wild animals, including deers, foxes and racoons; farm animals, livestock and fowl, including
10 horses, cattle, sheep, pigs, turkeys, ducks, and chickens, as well as any rodents.

[0062] The methods of the invention comprise administering an amount of Product R effective to promote wound healing, or treat loss of appetite or fatigue. An amount of Product R effective to promote wound healing, or treat loss of appetite or fatigue, within the meaning of the present invention can be determined by a patient's attending physician or
15 veterinarian. Such amounts are readily ascertained by one of ordinary skill in the art and can enable accelerated wound healing when administered in accordance with the present invention. Factors which influence what an amount of Product R effective to promote wound healing, or treat loss of appetite or fatigue, will be include, the specific activity of the therapeutic agent being used, the wound type (mechanical or thermal, full or partial
20 thickness, etc.), the size of the wound, the wound's depth (if full thickness), the absence or presence of infection, time elapsed since the injury's infliction, and the age, physical condition, existence of other disease states, and nutritional status of the patient.

Additionally, other medication the patient may be receiving will effect the determination of the amount of Product R to administer. In certain embodiments, the amount of Product R
25 effective to promote wound healing, or treat loss of appetite or fatigue, is in a range from about 0.5 microliters to about 100 microliters per kilogram of body weight per day, or from about 2.5 microliters to about 40 microliters per kilogram of body weight per day, or from about 10 microliters to about 25 microliters per kilogram of body weight per day. As used herein, "about" entails normal experimental variation. Alternatively, Product R may be
30 administered to the patient according to the conventional doses or any dosages that are apparent to a person of ordinary skill in the art.

[0063] The desired dose may be administered as two, three or more sub-doses at appropriate intervals, generally equally spread in time, throughout the day. The dosage used for topical administration to the wound will vary depending on the size and location of
35 the wound, and will preferably encompass the entire wound area.

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[0064] Typical routes of administration for Product R may include, without limitation, oral, topical, parenteral, sublingual, rectal, vaginal, ocular, and intranasal.

Parenteral administration includes subcutaneous injections, intravenous, intramuscular, intraperitoneal, intrapleural, intrasternal injection or infusion techniques. In a preferred embodiment of the invention, Product R is administered topically. In addition to direct topical application to the wound, Product R can be used systemically, by the subcutaneous route, to stabilize a wounded patient. It will be appreciated that the preferred route may vary with, for example, the condition and age of the recipient.

[0065] In certain embodiments, Product R is administered by both systemic and topical routes to promote the wound healing, or treat loss of appetite or fatigue,. First, systemic and topical administration of Product R can be used acutely to stabilize the wounded patient. Product R then can be used topically to promote wound healing, or treat loss of appetite or fatigue, as the patient is further stabilized, has undergone any necessary surgery to debride the wound, and has entered the recuperative phase.

[0066] The present invention also encompasses methods for promoting wound healing in a patient, comprising administering to said patient an amount of Product R effective to promote wound healing and an effective amount of another medicament. The present invention also encompasses methods for treating loss of appetite or fatigue in a patient, preferably a patient suffering from a wound or burn injury, comprising administering to said patient an amount of Product R effective to promote wound healing, or treat loss of appetite or fatigue, and an effective amount of another medicament. In certain embodiments, the other medicament is an antibiotic, a biological response modifier, *e.g.*, a cytokine, or a wound healing factor. Antibiotics useful in the methods of the invention include, but are not limited to, penicillin, cephalosporin, griseofulvin, bacitracin, polymyxin B, amphotericin B, erythromycin, neomycin, streptomycin, tetracycline, vancomycin, gentamicin, and rifamycin. Biological response modifiers useful in the methods of the invention include, but are not limited to, interferon- α , interferon- γ , interleukin-2, interleukin-4, interleukin-6, and tumor necrosis factor. Wound healing factors useful in the methods of the invention include, but are not limited to, interferon (IFN)- β , IFN- γ , interleukin (IL)-1, IL-2, IL-4, IL-5, IL-15, tumor necrosis factor, flt-1 ligand, arginine, connective tissue growth factor, adenosine, cyclic adenosine monophosphate, the fibroblast growth factor family, tumor growth factor- α , tumor growth factor- β (1 and 2), vascular endothelial growth factor, the epidermal growth factor family, the platelet derived growth factor family, the insulin-like growth factor family, nitric oxide, macrophage-stimulating protein, and macrophage-derived growth factor.

[0067] As used herein, the term “in combination” refers to the use of more than one prophylactic and/or therapeutic agents. The use of the term “in combination” does not restrict the order in which prophylactic and/or therapeutic agents are administered to a subject with a disorder. A first prophylactic or therapeutic agent can be administered prior to (e.g., up to 1 minute, 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., up to 1 minute, 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 to a subject which had, has, or is susceptible to a wound. The prophylactic or therapeutic agents are administered to a subject in a sequence and within a time interval such that the agent of the invention can act together with the other agent to provide an increased benefit than if they were administered otherwise. Any additional prophylactic or therapeutic agent can be administered in any order with the other additional prophylactic or therapeutic agents.

4.3. Monitoring of Effects During Therapy

[0068] The effects/efficacy of treatment of a wound according to the present invention can be detected, for example, on the level of the molecular and cellular agents involved in the immune response (e.g., macrophages, B cells, or T cells) or on the level of an affected tissue including, but not limited to, stimulation of macrophages to secrete growth factors, synthesis and cross-linking of collagen, and decrease in wound size, using standard methods well known to one of ordinary skill in the art.

4.4. Pharmaceutical Formulations

[0069] While it is possible for Product R to be administered as part of a pharmaceutical formulation, it is preferable to present it alone, although it may be administered at about the same time as one or more other pharmaceuticals are independently administered. If Product R is administered as part of a pharmaceutical formulation, the formulations of the present invention comprise at least one administered ingredient, *i.e.*, Product R, as above defined, together with one or more acceptable carriers thereof and optionally one or more additional medicaments. Suitable additional medicaments are provided in Section 4.2. The carrier(s) must be “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of the formulation

and not deleterious to the recipient thereof (e.g., suitable for *in vivo* use, in the patient).

Preferably, Product R in a pharmaceutical formulation is sterile.

[0070] The formulations may conveniently be presented in unit-dose or multi-dose containers, e.g., sealed ampules and vials. Preferred unit dosage formulations are those containing a daily dose or unit, daily sub-dose, or an appropriate fraction of the administered ingredient.

[0071] The compositions of the invention can be in the form of a solid, liquid or gas (aerosol). Pharmaceutical compositions of the invention can be formulated so as to allow a compound of the invention to be bioavailable upon administration of the composition to a subject. Compositions can take the form of one or more dosage units, where for example, a tablet can be a single dosage unit, and a container of a compound of the invention in aerosol form can hold a plurality of dosage units. A syringe containing a unit dose of Product R is also provided.

[0072] For oral administration, the pharmaceutical preparation can be in liquid form, for example, solutions, syrups or suspensions, or can be presented as a drug product for reconstitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The pharmaceutical compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinyl pyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets can be coated by methods well-known in the art.

[0073] Preparations for oral administration can be suitably formulated to give controlled release of the active compound.

[0074] For buccal administration, the compositions can take the form of tablets or lozenges formulated in conventional manner.

[0075] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide

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

5 [0076] The compounds can be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending,
10 stabilizing and/or dispersing agents. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[0077] The compounds can be formulated in compositions such as creams, lotions, gels, ophthalmic drops, ointments, solutions, suspensions, shampoos, or other forms known to one of skill in the art and described in, for example, Remington's Pharmaceutical
15 Sciences, 16th and 18th eds., Mack Publishing, Easton Pa. (1980 & 1990), and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia (1985). Actual methods for preparing pharmaceutical compositions are known or apparent to those skilled in the art and are described in detail in, for example, Remington's Pharmaceutical Sciences, 16th and 18th eds., Mack Publishing, Easton Pa. (1980 & 1990).

20 [0078] The compounds can also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

[0079] In addition to the formulations described previously, the compounds can also be formulated as a depot preparation. Such long acting formulations can be administered by
25 implantation (*e.g.*, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (*e.g.*, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophilic drugs.

30 4.5. Kits

[0080] The invention also provides kits for carrying out the methods and/or therapeutic regimens of the invention. In one embodiment, such kits comprise in one or more containers, Product R. In another embodiment, such kits comprise in one or more containers an amount of Product R effective to promote wound healing, or treat loss of
35 appetite or fatigue, in pharmaceutically acceptable form.

[0081] Product R in a container of a kit of the invention may be in the form of a pharmaceutically acceptable solution, *e.g.*, in combination with sterile saline, dextrose solution, or buffered solution, or other pharmaceutically acceptable sterile fluid.

Alternatively, Product R may be lyophilized or desiccated; in this instance, the kit
5 optionally further comprises in a container a pharmaceutically acceptable solution (*e.g.*, saline, dextrose solution, etc.), preferably sterile, to reconstitute Product R to form a solution for injection purposes.

[0082] In another embodiment, a kit of the invention further comprises a needle or syringe, preferably packaged in sterile form, for injecting Product R, and/or a packaged
10 alcohol pad. Instructions are optionally included for administration of Product R by a clinician or by the patient.

[0083] Kits are also provided for carrying out the combination therapies of the present invention. In one embodiment, a kit comprises a first container containing Product R and a second container containing an additional medicament. Suitable additional
15 medicaments are provided in Section 4.2.

[0084] The kit may for example comprise metal or plastic foil, such as a blister pack. The kit may be accompanied by one or more reusable or disposable device(s) for administration (*e.g.*, syringes, needles, dispensing pens) and/or instructions for administration.

20 4.6. Animal models

[0085] Animal models can optionally be used to demonstrate use of particular formulations and/or dosages of Product R in wound healing. Suitable animal models for wound healing are known to one of ordinary skill in the art.

25 [0086] The following examples only serve to further illustrate, but not to limit the scope of the present invention.

5. EXAMPLES

5.1. Example 1: Method for Preparing Product R

[0087] About 35.0 g of casein, about 17.1 g of beef peptone, about 22.0 g of
30 nucleic acid (RNA), about 3.25 g bovine serum albumin were suspended in about 2.5 liters of water for injection USP at about 3 to 7°C in a suitable container and gently stirred until all the ingredients have been properly wet. About 16.5 g of sodium hydroxide (reagent grade ACS) is added with stirring. Stirring is continued until the sodium hydroxide is completely dissolved. The reaction is autoclaved at about 9 lbs pressure and 200-230 °F for

a period of time until RNA is completely digested, for example, about 4 hours. At the end of the period, the autoclave was stopped and the reaction flask and contents were permitted to slowly cool to ambient temperature. The reaction was then cooled for at least six hours at about 3-8° C. The resulting solution was filtered through 2 micron and 0.45 micron filters using an inert gas such as nitrogen or argon at low pressure (1-6 psi). In a similar manner, the solution was filtered again through 0.2 micron pyrogen retention filters. The resulting filtrate was sampled and assayed for total nitrogen. A calculation was then performed to determine the quantity of cooled water for injection to be added to the filtrate to yield a diluted filtrate with a nitrogen content between about 165-210 mg/100 ml, the final volume is approximately 5 liters. The pH was then adjusted with either concentrated HCl (reagent grade ACS) or 1.0 normal NaOH to about 7.3-7.6. The diluted solution was then filtered again through 0.2 micron filters with inert gas at low pressure. The final filtrate was then filled and sealed into 2 ml glass ampoules or 2mL vials while in an inert gas atmosphere. The ampoules or vials were collected and autoclaved for final sterilization at 240° F and 20 to 30 psi pressure for about 30 minutes. Following the sterilization cycle, the ampoules with Product R were cooled and washed.

[0088] All quantities are subject to plus or minus 2.5% variation for pH, volume, and analytical adjustments.

5.2. Example 2

[0089] The patient was an 85 year old active male suffering from a chronic skin ulcer on the right leg due to venous insufficiency. The patient generally enjoyed good health. He has a history of chronic iron deficiency anemia on the basis of small amounts of bleeding from the bowel due to small arterio-venous malformations.

[0090] The patient previously had bilateral vein strippings of the lower extremities for varicose veins. Prior to Product R treatment, the patient developed a superficial skin ulcer under the lateral malleolus of the right tibia. He applied ointments and creams such as antibiotic ointments and zinc oxide cream. The lesion would heal with formation of an eschar but then the ulcer would re-open.

[0091] Product R was applied topically to the open lesion, which measured 3/8 inch, twice a day by dropping liquid Product R on the lesion from an insulin syringe. Within seven days, the chronic ulcer epithelialized and healed.

[0092] The lesion did not open and remained closed after three weeks of follow-up. This was the first time that this lesion had totally epithelialized. Although there is a depression in the skin at the site of the lesion, the color of the new skin over the area of the lesion is normal.

~~PCT/US2005/030798~~
5.3. Example 3

[0093] The patient was an 89 year old woman who was in her usual state of good health until she began to suffer from mild mental disorders, including a vacant look for variable periods, falling asleep at odd times and decreased ability to perform daily acts of living. Her appetite remained intact and she continued to interact socially.

[0094] When her physical condition began to deteriorate and she lost her appetite, physical therapy was begun. Subsequently, she developed a movement disorder requiring therapy with a sedative.

[0095] Prior to Product R therapy, a bulge was noted over her left hip; X-ray showed only a bone deformity. A month later, the overlying skin began to open and a foul smelling wound developed. Initially the wound was long and narrow. The wound was diagnosed by her physician as a decubitus ulcer. Treatment with antibiotics and Varihesive (ConvaTec, Skillman, NJ) did not affect the wound.

[0096] Treatment with Varihesive Hydrogel was also without effect. Her physical condition continued to deteriorate and she developed signs of cachexia with weight loss, reaching a weight of 35 kilograms. Over the next month, the wound enlarged to 3 times the initial size both in length and depth; the maximum diameter of the wound was now 10 cm in length and 4 cm in width. The underlying bones and tendons showed through the wound but the patient was without pain. The wound extended under the margins of the skin allowing a hand to be placed underneath the skin of the wound. A month prior to Product R treatment, eschars began to form on the patient's back but they did not ulcerate. At the time when Product R therapy was initiated, two smaller decubitus ulcers appeared in the sacral area.

[0097] Topical therapy was initially initiated with Product R. 1ml of Product R was applied to the wound twice a day; the patient continued with antibiotic therapy. Two weeks after the initiation of Product R therapy the wound showed improvement and was beginning to close.

[0098] Due to the continued lack of appetite, and the resulting cachexia, systemic therapy with Product R by subcutaneous injection of 1ml once a day was initiated two months later. Within two weeks of initiation of systemic AVR118 therapy, the patient showed marked improvement in appetite and her general physical condition. She began to gain weight, was mentally more alert and began to interact with her environment. She grew new hair whereas she had been losing hair before Product R therapy was initiated.

[0099] Both topical and systemic therapy (1ml subcutaneously 3 times per week) with Product R was continued. The patient continued to show improvement and the large

decubitus ulcer is considerably decreased in size. Especially noteworthy, the decubitus ulcer has filled in with healthy looking granulation tissue. The margins of the wound are no longer detached from the underlying tissue so that a hand no longer can be placed under the skin of the wound. From the beginning time point when Product R therapy was initiated, to
5 eight months subsequently, the length of the wound decreased from 10 cm to approximately 4 1/2 cm. The two smaller decubitus ulcers have closed and healed. The patient has shown marked increase in her mental awareness and her general physical condition, including her appetite, greatly improved. The patient suffered no side effects from either topical or systemic therapy with Product R. The patient is maintaining treatment with Product R
10 topically to the wound and by subcutaneous injection.

[00100] The present invention is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of
15 the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

[00101] Various references are cited herein, including scientific publications, patent
20 applications, and patents, the disclosures of which are incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. A method of promoting wound healing in a patient comprising administering to a patient in need of wound healing an amount of Product R effective to promote wound healing, wherein said Product R comprises nucleotides and peptides having molecular weights not more than 14 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4 ($\pm 10\%$) at 260 nm/230 nm.
2. The method of claim 1, wherein the patient is human.
3. The method of claim 1, wherein the amount of Product R is in a range from about 0.5 microliters to about 100 microliters per kilogram of body weight per day.
4. The method of claim 1, wherein the amount of Product R is in a range from about 2.5 microliters to about 40 microliters per kilogram of body weight per day.
5. The method of claim 1, wherein the amount of Product R is in a range from about 10 microliters to about 25 microliters per kilogram of body weight per day.
6. The method of claim 1, wherein the Product R is administered parenterally, topically or systemically.
7. The method of claim 1, wherein the Product R is administered topically to a wound in a dose adequate to encompass the total area of the wound.
8. The method of claim 1, wherein the wound is a result of decubitus ulcer, diabetic ulcer, surgical wound, or burn injury.
9. The method of claim 1, further comprising administering to the patient an effective amount of an antibiotic, biological response modifier, or a wound healing factor.
10. The method of claim 1, further comprising administering to the patient an effective amount of a biological response modifier, wherein the biological response modifier is selected from the group consisting of interferon- α , interferon- γ , interleukin-2, interleukin-4, interleukin-6, and tumor necrosis factor.
11. The method of claim 1, further comprising administering to the patient an effective amount of a wound healing factor, wherein the wound healing factor is selected from the group consisting of interferon- β , interferon- γ , interleukin (IL)-1, IL-2, IL-4, IL-5, IL-15, tumor necrosis factor, flt-1 ligand, arginine, connective tissue growth factor, adenosine, cyclic adenosine monophosphate, the fibroblast growth factor family, tumor growth factor- α , tumor growth factor- β (1 and 2), vascular endothelial growth factor, the epidermal growth factor family, the platelet derived growth factor family, the insulin-like

growth factor family, nitric oxide, macrophage-stimulating protein, and macrophage-derived growth factor.

12. A method of treating loss of appetite or fatigue in a patient, preferably a patient suffering from a wound or burn injury, comprising administering to a patient in need of treatment an amount of Product R effective to treat loss of appetite or fatigue, wherein said Product R comprises nucleotides and peptides having molecular weights not more than 14 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4 ($\pm 10\%$) at 260 nm/230 nm.
13. The method of claim 12, wherein the patient is human.
14. The method of claim 12, wherein the amount of Product R is in a range from about 0.5 microliters to about 100 microliters per kilogram of body weight per day.
15. The method of claim 12, wherein the amount of Product R is in a range from about 2.5 microliters to about 40 microliters per kilogram of body weight per day.
16. The method of claim 12, wherein the amount of Product R is in a range from about 10 microliters to about 25 microliters per kilogram of body weight per day.
17. The method of claim 12, wherein the Product R is administered parenterally, topically or systemically.
18. The method of claim 12, wherein the Product R is administered topically to a wound in a dose adequate to encompass the total area of the wound.
19. The method of claim 12, wherein the wound is a result of decubitus ulcer, diabetic ulcer, surgical wound, or burn injury.
20. The method of claim 12, further comprising administering to the patient an effective amount of an antibiotic, biological response modifier, or a wound healing factor.
21. The method of claim 12, further comprising administering to the patient an effective amount of a biological response modifier, wherein the biological response modifier is selected from the group consisting of interferon- α , interferon- γ , interleukin-2, interleukin-4, interleukin-6, and tumor necrosis factor.
22. The method of claim 12, further comprising administering to the patient an effective amount of a wound healing factor, wherein the wound healing factor is selected from the group consisting of interferon- β , interferon- γ , interleukin (IL)-1, IL-2, IL-4, IL-5, IL-15, tumor necrosis factor, flt-1 ligand, arginine, connective tissue growth factor, adenosine, cyclic adenosine monophosphate, the fibroblast growth factor family, tumor growth factor- α , tumor growth factor- β (1 and 2), vascular endothelial growth factor, the

epidermal growth factor family, the platelet derived growth factor family, the insulin-like growth factor family, nitric oxide, macrophage-stimulating protein, and macrophage-derived growth factor.

23. A pharmaceutical composition comprising 1) an amount of Product R effective to promote wound healing; 2) a biological response modifier; and 3) a pharmaceutically acceptable carrier, wherein the biological response modifier is selected from the group consisting of interleukin-2, interleukin-4, interleukin-6, and tumor necrosis factor, and wherein said Product R comprises nucleotides and peptides having molecular weights not more than 14 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4 ($\pm 10\%$) at 260 nm/230 nm.

24. A pharmaceutical composition comprising 1) an amount of Product R effective to promote wound healing; 2) a wound healing factor; and 3) a pharmaceutically acceptable carrier, wherein the wound healing factor is selected from the group consisting of interleukin (IL)-1, IL-2, IL-4, IL-5, IL-15, tumor necrosis factor, flt-1 ligand, arginine, connective tissue growth factor, adenosine, cyclic adenosine monophosphate, the fibroblast growth factor family, tumor growth factor- α , tumor growth factor- β (1 and 2), vascular endothelial growth factor, the epidermal growth factor family, the platelet derived growth factor family, the insulin-like growth factor family, nitric oxide, macrophage-stimulating protein, and macrophage-derived growth factor, and wherein said Product R comprises nucleotides and peptides having molecular weights not more than 14 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4 ($\pm 10\%$) at 260 nm/230 nm.

25. A kit comprising a first container which contains an amount of Product R effective to promote wound healing and a second container which contains an antibiotic, biological response modifier, or a wound healing factor, and wherein said Product R comprises nucleotides and peptides having molecular weights not more than 14 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4 ($\pm 10\%$) at 260 nm/230 nm.

26. A kit comprising a first container which contains an amount of Product R effective to promote wound healing and a second container which contains a biological response modifier, wherein the biological response modifier is selected from the group

consisting of ~~interferon- α , interferon- γ~~ , interleukin-2, interleukin-4, interleukin-6, and tumor necrosis factor, and wherein said Product R comprises nucleotides and peptides having molecular weights not more than 14 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said

5 composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4 ($\pm 10\%$) at 260 nm/230 nm.

27. A kit comprising a first container which contains an amount of Product R effective to promote wound healing and a second container which contains a wound healing factor, wherein the wound healing factor is selected from the group consisting of

10 interferon- β , interferon- γ , interleukin (IL)-1, IL-2, IL-4, IL-5, IL-15, tumor necrosis factor, flt-1 ligand, arginine, connective tissue growth factor, adenosine, cyclic adenosine monophosphate, the fibroblast growth factor family, tumor growth factor- α , tumor growth factor- β (1 and 2), vascular endothelial growth factor, the epidermal growth factor family, the platelet derived growth factor family, the insulin-like growth factor family, nitric oxide,

15 macrophage-stimulating protein, and macrophage-derived growth factor, and wherein wherein said Product R comprises nucleotides and peptides having molecular weights not more than 14 KDa, wherein said nucleotides and peptides are breakdown products of casein, peptone, RNA and serum albumin, and wherein said composition has a light absorption spectrum with typical absorption ratios of 2.0 ($\pm 10\%$) at 260 nm/280 nm and 1.4

20 ($\pm 10\%$) at 260 nm/230 nm.

SEQUENCE LISTING

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Cohen, Mathew

<120> METHODS FOR PROMOTING WOUND HEALING

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