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(54) **Title**: APPARATUSES, METHODS, AND COMPOSITIONS FOR THE TREATMENT AND PROPHYLAXIS OF CHRONIC WOUNDS

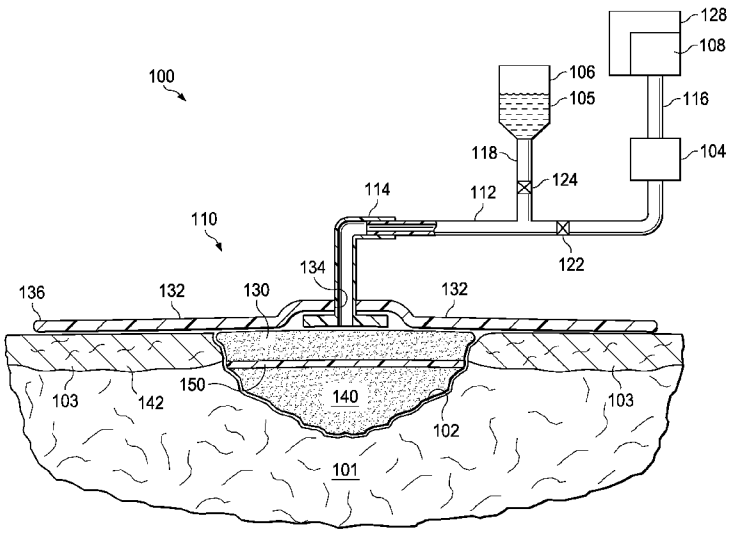

FIG. 1

(57) **Abstract**: According to an illustrative embodiment a method to promote healing of a wound is provided comprising contacting the wound with a biologically active composition comprising a lipoic acid derivative and gelatin. In another embodiment a wound dressing is provided comprising a scaffold coated with a biologically active composition comprising a lipoic acid derivative. In a further embodiment, a system is provided for treating a tissue site of a patient, the system comprising a reduced-pressure source to supply reduced pressure, a manifold to distribute reduced pressure to a tissue site and a scaffold coated with a biologically active composition comprising a lipoic acid derivative. Methods for producing such a system and scaffold are also disclosed.

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TITLE OF THE INVENTION

APPARATUSES, METHODS, AND COMPOSITIONS FOR THE TREATMENT AND PROPHYLAXIS OF CHRONIC WOUNDS

BACKGROUND

[0001] The present invention relates generally to medical treatment systems, and more particularly, medical dressings, systems, and methods employing alpha-lipoic acid and its pharmaceutically acceptable salts and derivatives, for the preparation and composition applied to a substrate for treatment or prophylaxis of chronic wounds.

[0002] Typical procedures for treating chronic wounds such as, for example, venous ulcers, diabetic ulcers and pressure sores, include the use of absorbent dressings or hydrocolloid gels. Additionally, since most chronic wounds are infected, many wound dressings contain antimicrobial agents, such as silver or iodine, to either create a barrier to microorganisms or reduce microbial load. These treatments are used more for managing the wound environment and moisture balance than actively promoting wound healing.

[0003] Inflammation and the timely release of reactive oxygen species (ROS) are critical for normal wound repair and, together with proteolytic and other cytotoxic enzymes, serve to kill ingested bacteria and prevent wound infection. However, due to other circumstances such as patient nutrition, co-morbidities (smoking, diabetes), or poor blood circulation due to patient positioning, the inflammatory phase may last too long resulting in the creation of excess ROS that actually damage surrounding tissue including healthy tissue forming within the wound. Excess ROS, also known as "free radicals," can be detrimental to tissue because they also damage cells and extracellular matrix components such as collagen. Additionally, ROS can act as signaling molecules to recruit matrix metallo proteases (MMPs) and other proteases to the wound site. Normal endogenous levels of MMPs are essential for tissue remodeling during the wound healing process. However, in excess, they continually break down the new tissue that is formed. This leads to a wound that either does not heal quickly or becomes "stalled." Excess levels of ROS and MMPs create a sustained state of inflammation thereby preventing the progression of normal wound healing.

[0004] Elevated levels of MMPs have been remedied by preventing activation of MMPs or by use of MMP inhibitors. Some wound dressings on the market use various forms of natural collagen as a sacrificial substrate for MMPs because the collagen also provides the mechanical properties (integrity) necessary to form the dressing. Topical application of antioxidants to a wound may reduce ROS levels, subsequently helping a chronic wound to re-enter a normal healing state.

SUMMARY

[0005] According to an illustrative embodiment, a method for promoting healing of a wound is provided comprising contacting a wound site with a biologically active composition comprising a lipoic acid derivative and, optionally, gelatin. Biologically active compositions, such as those provided, may be formulated for example as a solution, a cream or a gel. In certain aspects, a biologically active composition is coated on the surface of a wound dressing (*e.g.,* a porous scaffold), which can be positioned at a wound site. Methods for producing a scaffold coated with a biologically active composition are also provided.

[0006] According to another illustrative embodiment, a system is provided for treating a wound at a tissue site of a patient that includes a reduced-pressure source to supply reduced pressure, a distribution manifold, and a scaffold adapted for placement adjacent the wound. The system also includes a drape to cover the sealant and further form the substantially sealed space. The scaffold is coated with a biologically active composition including a lipoic acid derivative or any of its pharmaceutically acceptable salts and derivatives for treatment or prophylaxis of chronic wounds. The scaffold may also comprise a collagen coating such a coating comprising gelatin.

[0007] According to another illustrative embodiment, an apparatus includes a distribution manifold and a scaffold adapted for placement adjacent the wound. The scaffold is coated with a biologically active composition including a lipoic acid derivative or any of its pharmaceutically acceptable salts and derivatives.

[0008] According to another illustrative embodiment, a method for treating a tissue site of a patient includes applying a dressing to the wound. A dressing may include a composition comprising a lipoic acid derivative and, optionally, gelatin. The dressing

includes, in some aspects, a distribution manifold and a scaffold adapted for placement adjacent the wound. In certain embodiments, the dressing also includes a drape for covering the dressing and further forming the substantially sealed space.

[0009] The present invention provides the use of alpha-lipoic acid and its pharmaceutically acceptable salts and derivatives, for the preparation of a composition for treatment or prophylaxis of chronic wounds. In certain aspects, a lipoic acid derivative is formulated with gelatin in a composition for treating a wound.

[0010] In a further embodiment, the invention provides a kit or pouch comprising wound dressing components. Such a kit can, for example, comprise one or more of a wound dressing comprising a biologically active composition including alpha-lipoic acid and, optionally, gelatin, a drape, a reduced pressure manifold, one or more fluid conduits (*e.g.,* tubes) and instructions for use of the kit components. In certain aspects, the components of the kit or pouch are sterilized, for example by gamma irradiation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. 1 is a schematic, cross-sectional view of a reduced-pressure treatment system including wound dressing that utilizes a first distribution manifold according to one illustrative embodiment;

[0012] FIG. 2 is a schematic, cross-sectional view of the reduced-pressure treatment system of FIG. 1 including wound dressing that utilizes a second distribution manifold according to another illustrative embodiment;

[0013] FIG. 3 is a schematic, cross-sectional view of the reduced-pressure treatment system of FIG. 1 including wound dressing that utilizes a third distribution manifold according to another illustrative embodiment;

[0014] FIG. 4A illustrates a method of promoting new tissue growth at a tissue site according to one embodiment;

[0015] FIG. 4B depicts a method of promoting new tissue growth at a tissue site according to another embodiment;

[0016] FIG. 5 illustrates a front view of a tissue growth kit according to an embodiment of the present invention;

[0017] FIG. 6A is a chemical formula of certain derivatives of alpha-lipoic acid or pharmaceutically acceptable salts or derivatives thereof;

[0018] FIG. 6B is a chemical formula of other derivatives of alpha-lipoic acid or pharmaceutically acceptable salts or derivatives thereof;

[0019] FIG. 7 is a graph showing antioxidant activity for scaffolds containing alpha-lipoic acid;

[0020] FIG. 8 is a chart showing the reduction of MMP activity for scaffolds containing alpha-lipoic acid and gelatin as compared to controls; and

[0021] FIG. 9 is a chart showing the release profile of alpha-lipoic acid from coating on a scaffold.

DETAILED DESCRIPTION

[0022] In the following detailed description of the illustrative embodiments, reference is made to the accompanying drawings that form a part hereof. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is understood that other embodiments may be utilized and that logical structural, mechanical, electrical, and chemical changes may be made without departing from the spirit or scope of the invention. To avoid detail not necessary to enable those skilled in the art to practice the embodiments described herein, the description may omit certain information known to those skilled in the art. The following detailed description is, therefore, not to be taken in a limiting sense, and the scope of the illustrative embodiments are defined only by the appended claims.

[0023] The term "reduced pressure" as used herein generally refers to a pressure less than the ambient pressure at a tissue site that is being subjected to treatment. In most cases, this reduced pressure will be less than the atmospheric pressure at which the patient is located. Alternatively, the reduced pressure may be less than a hydrostatic pressure associated with tissue at the tissue site. Although the terms "vacuum" and "negative pressure" may be used to describe the pressure applied to the tissue site, the actual pressure reduction applied to the tissue site may be significantly less than the pressure reduction normally associated with a complete vacuum. Reduced pressure may initially generate fluid flow in the area of the tissue site. As the hydrostatic pressure around the tissue site approaches the desired reduced pressure, the flow may subside, and the reduced pressure is then maintained. Unless otherwise indicated, values of pressure stated herein are gauge pressures. Similarly, references to increases in reduced pressure typically refer to a decrease in absolute pressure, while decreases in reduced pressure typically refer to an increase in absolute pressure.

[0024] The term "tissue site" as used herein includes, without limitation, a wound or defect located on or within any tissue, including but not limited to, bone tissue, adipose tissue, muscle tissue, neural tissue, dermal tissue, vascular tissue, connective tissue, cartilage, tendons, or ligaments. The term "tissue site" may further refer to areas of any tissue that are not necessarily wounded or defective, but are instead areas in which it is desired to add or promote the growth of additional tissue. For example, reduced pressure tissue treatment may be used in certain tissue areas to grow additional tissue that may be harvested and transplanted

to another tissue location. The tissue may be that of any mammal, such as a mouse, rat, rabbit, cat, dog, pig, or primate, including humans, that are being treated as patients. Also, the wound at the tissue site may be due to a variety of causes, including trauma, surgery, degeneration, and other causes.

[0025] The term "biologically active composition" as used herein refers to a composition formulated with a lipoic acid derivative and, optionally, a gelatin. Such compositions may be formulated in any pharmaceutically acceptable carrier and will typically comprise an amount of lipoic acid derivative effective to reduce reactive oxygen species and inflammation at a tissue site. Gelatin for use according to the invention may be from any tissue source, such as from bovine, equine, or porcine tissues. Formulations and components for biologically active compositions are further detailed below.

[0026] Referring to FIGs. 1 and 2, a reduced pressure treatment system 100 for applying a reduced pressure to a tissue site 101 of a patient according to an illustrative embodiment where the tissue site includes wound 102 surrounded by healthy tissue including, without limitation, the epidermis 103 of such tissue. The system 100 comprises a canister 104 having a filter (not shown) contained within the canister 104 and a fluid supply 106 for delivering fluid 105 to the tissue site 101. The canister 104 is positioned in fluid communication with a reduced pressure source 108 and a reduced pressure dressing 110 that is positioned at the tissue site 101. The reduced pressure dressing 110 is fluidly connected to the canister 104 by a first conduit 112. The first conduit 112 may fluidly communicate with the reduced pressure dressing 110 through a tubing adapter 114. A second conduit 116 fluidly connects the canister 104 with the reduced pressure source 108.

[0027] The canister 104 may be a fluid reservoir, or collection member, to filter or hold exudates and other fluids removed from the tissue site 101. In one embodiment, the canister 104 and the reduced-pressure source 108 are integrated into a single housing structure. The fluid supply 106 is fluidly connected to the reduced pressure dressing 110 by a third conduit 118 that may be connected directly to the reduced pressure dressing 110 (not shown) or indirectly via the first conduit 112 which requires valves 122 and 124 for controlling the delivery of reduced pressure from the reduced pressure source 108 and/or fluid 105 from the fluid supply 106, respectively. The fluid 105 may be any gas or liquid, and may contain

growth factors, healing factors, or other substances to treat the wound 102 at the tissue site 101. For example, the fluid 105 may be water, saline, or dye saline.

[0028] In the embodiment illustrated in FIG. 1, the reduced pressure source 108 is an electrically-driven vacuum pump. In another implementation, the reduced pressure source 108 may instead be a manually-actuated or manually-charged pump that does not require electrical power. The reduced pressure source 108 instead may be any other type of reduced pressure pump, or alternatively a wall suction port such as those available in hospitals and other medical facilities. The reduced pressure source 108 may be housed within or used in conjunction with a reduced pressure treatment unit 128, which may also contain sensors, processing units, alarm indicators, memory, databases, software, display unites, and user interfaces that further facilitate the application of reduced pressure treatment to the tissue site 101. In one example, a sensor or switch (not shown) may be disposed at or near the reduced pressure source 108 to determine a source pressure generated by the reduced pressure source 108. The sensor may communicate with a processing unit that monitors and controls the reduced pressure that is delivered by the reduced pressure source 108.

[0029] The reduced pressure dressing 110 includes a distribution manifold 130 adapted to be positioned at the tissue site 101, and a drape 132 that covers the distribution manifold 130 to maintain reduced pressure beneath the drape 132 at the tissue site 101. The reduced pressure dressing 110 may also include a separate scaffold 140, wherein the scaffold is coated with a biologically active composition comprising a lipoic acid derivative, and is positioned within the wound 102 in fluid communication with the distribution manifold 130. The system may further include a release layer 150 positioned in fluid communication between the distribution manifold 130 and the scaffold 140. The release layer 150 may include a release material such as a hydro-gel foaming material or water-soluble polymer. The drape 132 includes an aperture 134 through which the tubing adapter 114 extends to provide fluid communication between the conduit 112 and the distribution manifold 130. The drape 132 further includes a periphery portion 136 that may extend beyond a perimeter of the tissue site 101 and may include an adhesive or bonding agent (not shown) to secure the drape 132 to tissue adjacent the tissue site 101. In one embodiment, the adhesive disposed on the drape 132 may be used to provide a seal between the epidermis 103 and the drape 132 to prevent leakage of reduced pressure from the tissue site 101. In another embodiment, a seal layer (not shown)

such as, for example, a hydrogel or other material may be disposed between the drape 132 and the epidermis 103 to augment or substitute for the sealing properties of the adhesive.

[0030] The drape 132 may be any material that provides a pneumatic or fluid seal. The drape 132 may, for example, be an impermeable or semi-permeable, elastomeric material. "Elastomeric" means having the properties of an elastomer, and generally refers to a polymeric material that has rubber-like properties. More specifically, most elastomers have elongation rates greater than 100% and a significant amount of resilience. The resilience of a material refers to the material's ability to recover from an elastic deformation. Examples of elastomers may include, but are not limited to, natural rubbers, polyisoprene, styrene butadiene rubber, chloroprene rubber, polybutadiene, nitrile rubber, butyl rubber, ethylene propylene rubber, ethylene propylene diene monomer, chlorosulfonated polyethylene, polysulfide rubber, polyurethane, EVA film, co-polyester, and silicones. Specific examples of drape materials include a silicone drape, 3M Tegaderm® drape, acrylic drape such as one available from Avery Dennison, or an incise drape.

[0031] Referring to FIG. 2, another embodiment of the reduced pressure dressing 110 is shown wherein the conduit connector 114 that penetrates the drape 132 is replaced by a perforated tube 113 having a plurality of apertures 115 in one end that are in fluid communication with the distribution manifold 130. The first conduit 112 is fluidly coupled to the other end of the perforated tube 113 for delivering reduced pressure or other fluids to the wound 102 as described above via the distribution manifold 130 and the scaffold 150. The distribution manifold 130 of the reduced pressure dressing 110 may be adapted to fully contact (not shown) or partially contact the wound 102 of the tissue site 101 being treated by the reduced pressure dressing 110, in which case the scaffold 140 covers the remaining portion of the wound 102.

[0032] In another embodiment shown in FIG. 3, the distribution manifold 130 of the reduced pressure dressing 110 contacts only the scaffold 140 but not any portion of the wound 102. In this embodiment, the first conduit 112 delivers reduced pressure or other fluids via the distribution manifold 130 to the scaffold 140 and ultimately the wound 102. In either embodiment, the distribution manifold 130 and the scaffold 140 may be any size, shape, or thickness depending on a variety of factors, such as the type of treatment being implemented or the nature and size of the tissue site 101 or the wound 102. For example, the size and shape

of the scaffold 140 may be customized by a user to fill or partially fill the tissue site 101 or the wound 102. The distribution manifold 130 may have, for example, a square shape, or may be shaped as a circle, oval, polygon, an irregular shape, or any other shape.

[0033] The distribution manifold 130, scaffold 140, and the release layer 150 (collectively referred to as the "layers") all include a plurality of flow channels of sufficient size to allow distribution of reduced pressure within the reduced pressure dressing 110 and to the wound 102. The flow channels provided in each of the layers may be an inherent characteristic of the material provided in that layer (*e.g.,* a naturally porous material), or the flow channels may be chemically, mechanically, or otherwise formed in the material prior to or after assembly of the three layers. The placement of the layers adjacent one another allows the flow channels in one layer to fluidly communicate with the flow channels in the adjacent layer. For example, the relative positioning or connection of the layers as described above allow the plurality of flow channels of the scaffold 140 to fluidly communicate with the plurality of flow channels of the release layer 150, which are capable of fluidly communicating with the plurality of flow channels of the distribution manifold 130.

[0034] The term "manifold" as used herein generally refers to a substance or structure that is provided to assist in applying reduced pressure to, delivering fluids to, or removing fluids from a tissue site. A manifold typically includes a plurality of flow channels or pathways that are interconnected to improve distribution of fluids provided to and removed from the area of tissue around the manifold. Examples of manifolds may include without limitation devices that have structural elements arranged to form flow channels, cellular foam such as open-cell foam, porous tissue collections, and liquids, gels and foams that include or cure to include flow channels. In one illustrative embodiment, the distribution manifold 130 is a foam material that distributes reduced pressure to the tissue site 101 when the distribution manifold 130 is in contact with or near the tissue site 101. The foam material may be either hydrophobic or hydrophilic.

[0035] In one non-limiting example, the distribution manifold 130 is an open-cell, reticulated polyurethane foam such as GranuFoam® dressing available from Kinetic Concepts, Inc. of San Antonio, Texas. In the example in which the distribution manifold 130 is made from a hydrophilic material, the distribution manifold 130 also functions to wick fluid away from the tissue site 101, while continuing to provide reduced pressure to the tissue site 101 as

a manifold. The wicking properties of the distribution manifold 130 draw fluid away from the tissue site 101 by capillary flow or other wicking mechanisms. To adequately distribute the reduced pressure and wick fluid away from the tissue site 101, the GranuFoam® dressing in one embodiment has a porosity with pore sizes ranging from about 400-600 microns. An example of a hydrophilic foam is a polyvinyl alcohol, open-cell foam such as V.A.C. WhiteFoam® dressing available from Kinetic Concepts, Inc. of San Antonio, Texas. Other hydrophilic foams may include those made from polyether. Other foams that may exhibit hydrophilic characteristics include hydrophobic foams that have been treated or coated to provide hydrophilicity. In one embodiment, the distribution manifold 130 may be constructed from bioresorbable materials that do not have to be removed from a patient's body following use of the reduced pressure dressing 110. Suitable bioresorbable materials may include, without limitation, collagen or a polymeric blend of polylactic acid (PLA) and polyglycolic acid (PGA). The polymeric blend may also include, without limitation, polycarbonates, polyfumarates, and capralactones.

[0036] Scaffolds, such as scaffold 140 of FIGs. 1-3, may be formed from biologic or synthetic scaffold materials. Scaffolds are used in the field of tissue engineering to support protein adhesion and cellular ingrowth for tissue repair and regeneration. In certain aspects, a scaffold may further comprise a biologically active composition, such as those detailed herein (*e.g.,* a composition comprising a lipoic acid derivation and gelatin). The current state of the art in scaffold technology relies upon the inherent characteristics of the surrounding tissue space for the adsorption of proteins and migration of cells. The scaffold 140 provides physical guidance to direct the pathway of fluid flow within the wound 102 at the tissue site 101 creating avenues for the movement and migration of adhesive proteins and cells, respectively, which are integral to the establishment of a provisional matrix in predetermined patterns of organization within the tissue space. Within this context, scaffolds serve to refine the pathways of fluid flow within the tissue space to cellular level patterns from the fluid source to the point(s) of flow initiation within the distribution manifold 130. Thus, the scaffold 140 embodies characteristics of a manifold for refinement of the flow pathways within the wound 102 at the tissue site 101. In certain aspects, a scaffold is a reticulated structure comprising high void fraction for improved bioabsorption properties. Such high void fraction scaffold may also facilitate effective coating with biologically active compositions as detailed herein.

[0037] The distribution manifold 130 or portion thereof may further serve as a scaffold for new cell-growth, or a separate scaffold may be used in conjunction with the distribution manifold 130 to promote cell-growth as described above. Thus, a scaffold may also function as a manifold in accordance with the embodiments described herein to administer reduced pressure tissue treatment to a tissue site. Although one skilled in the art recognizes that the distribution manifold 130 may also function as a scaffold, the illustrative embodiments herein describe the use of a separate scaffold structure, the scaffold 140, in conjunction with the distribution manifold 130, wherein the scaffold also functions as a manifold. In such embodiments, the separate manifold may also be coated with a biologically active composition comprising a lipoic acid derivative. The scaffold and/or manifold may be also be infused with, coated with, or comprised of cells, growth factors, extracellular matrix components, nutrients, integrins, or other substances to promote cell growth.

[0038] In general a scaffold may be composed of any of the materials used to form a manifold. Nonlimiting examples of suitable scaffold materials include extracellular matrix proteins such as fibrin, collagen or fibronectin, and synthetic or naturally occurring polymers, including bioabsorbable or non-absorbable polymers, such as polylactic acid (PLA), polyglycolic acid (PGA), polylactide-co-glycolide (PLGA), polyvinylpyrrolidone, polycaprolactone, polycarbonates, polyfumarates, caprolactones, polyamides, polysaccharides (including alginates (*e.g.,* calcium alginate) and chitosan), hyaluronic acid, polyhydroxybutyrate, polyhydroxyvalerate, polydioxanone, polyorthoesthers, polyethylene glycols, poloxamers, polyphosphazenes, polyanhydrides, polyamino acids, polyacetals, polycyanoacrylates, polyurethanes (*e.g.,* GranuFoam®), polyacrylates, ethylene-vinyl acetate polymers and other acyl substituted cellulose acetates and derivatives thereof, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinylimidazole), chlorosulphonated polyolefins, polyethylene oxide, polyvinyl alcohol, Teflon®, and nylon. The scaffold can also comprise ceramics such as hydroxyapatite, coralline apatite, calcium phosphate, calcium sulfate, calcium carbonate or other carbonates, bioglass, allografts, autografts, xenografts, decellularized tissues, or composites of any of the above. In particular embodiments, the scaffold comprises collagen (*e.g.,* Biostep™ or Pomogran™ scaffolds), polylactic acid (PLA), polyglycolic acid (PGA), polylactide-co-glycolide (PLGA), a polyurethane, a polysaccharide, an hydroxyapatite, or a polytherylene glycol. Additionally, the scaffold can comprise

combinations of any two, three or more materials, either in separate or multiple areas of the scaffold, combined noncovalently or covalently (*e.g.*, copolymers such as a polyethylene oxide-polypropylene glycol block copolymers, or terpolymers), or combinations thereof. Suitable matrix materials are discussed in, for example, Ma and Elisseeff, 2005, and Saltzman, 2004. The scaffold 140 may be manufactured by any of the following processes: salt leaching, freeze-drying, phase-separation, weaving fibers, bonding non-woven fibers, foaming, or any other suitable manufacturing method for the selected material.

[0039] The scaffold 140 may be any porous, bioresorbable material that is capable of accepting and/or integrating new tissue growth into the scaffold 140 as described above. The pores of the scaffold 140 are preferably interconnected to define the plurality of flow channels within the scaffold 140, but additional flow channels may be provided by mechanically, chemically, or otherwise forming the flow channels within the scaffold 140. As further detailed below, the exterior and interior surfaces (*e.g.,* flow channels) of the scaffold may be coated with a biologically active composition comprising a lipoic acid derivative, and options gelatin. The pore sizes associated with the scaffold 140 are typically between about 50 and 500 microns, and more preferably between about 100 and 400 microns. Pore sizes below 50 microns tend to inhibit or prevent tissue growth. According, scaffolds for use according to the invention, comprise a pore size large enough such that pores remain larger than about 50 microns after the scaffold is coated with a biologically active composition. In one embodiment, the preferred average pore size of pores within the scaffold after coating is about 100 microns.

[0040] The release layer 150 minimizes points of contact between the distribution manifold 130 and the scaffold 140. In one embodiment, the release material 150 will prevent any contact between the distribution manifold 130 and the scaffold 140. By minimizing contact between the distribution manifold 130 and the scaffold 140, the release material 150 serves as a barrier to tissue in-growth from the scaffold 140 into the distribution manifold 130. The release layer 150 may also serve as a binder and a release agent for the distribution manifold 130 and the scaffold 140. The release layer 150 is preferably either a hydrogel-forming material or a water-soluble polymer. The hydrogel-forming material may be any suitable material that is capable of accepting and/or forming a liquid or gel-like substance after exposure to water or other fluids for a specified period of time.

[0041] The plurality flow channels of the release layer 150 allows the distribution of reduced pressure from the distribution manifold 130 to the scaffold 140, and further allows passage of any fluids being provided to or being removed from the wound 102. The plurality of flow channels may be an inherent characteristic of the release layer 150 (*i.e.* interconnected pores or other flow channels within the material itself), or mechanically, chemically, or otherwise formed in the release layer 150. Regardless of whether pores, voids, apertures, or some combination thereof are used to define the plurality of flow channels in the release layer 150, the porosity of the release layer 150 may be less than the porosity of the scaffold 140 to minimize in-growth of tissue into the release layer 150. The porosity of the release layer 150 may be controlled by limiting the size of the pores, voids, or apertures, or by controlling the number (*i.e.* density) of pores, voids, or apertures disposed in the release layer 150. The porosity of the release layer 150, however, must remain high enough to allow distribution of reduced pressure and the flow of fluids through the release layer 150.

[0042] In operation, the three layers of the reduced pressure dressing 110 are trimmed if necessary to match the shape and size of the wound 102. In many cases, the wound 102 may be an open wound, burn, or other-damaged tissue, but the tissue site 101 may similarly be a site that contains healthy tissue upon which it is desired to grow additional tissue. The reduced pressure dressing 110 is placed adjacent the wound 102 such that the scaffold 140 is in contact with the wound 102. The multiple layers of the reduced pressure dressing 110 may be laminated, bonded, or otherwise connected, but the layers may also be separate from one another. If certain of the layers are not connected to one another, the various layers may be placed individually such that the scaffold 140 is in contact with the tissue site, the release layer 150 is in contact with the scaffold 140, and the distribution manifold 130 is in contact with the release layer 150.

[0043] After positioning the reduced pressure dressing 110, a reduced pressure is delivered from the reduced pressure source 108 to the manifold 130. The reduced pressure is distributed through the plurality of flow channels associated with the manifold 130 to the plurality of flow channels associated with the release layer 150. The reduced pressure is then distributed to the plurality of flow channels associated with the scaffold 140. As reduced pressure reaches the wound 102, fluids at the wound 102 such as wound exudate may be drawn through the plurality of flow channels in all the layers and removed from the reduced

pressure dressing 110. The canister 104 collects exudate and protect the reduced pressure source 108. In addition to allowing distribution of reduced pressure and the withdrawal of fluids from the wound 102, the plurality of flow channels of the three layers may be used to distribute fluids such as irrigation fluids, medication, antimicrobials, antibacterials, antivirals, and growth factors to the wound 102.

[0044] The application of reduced pressure to the wound 102 induces new tissue growth. Some of the mechanisms by which new tissue growth is promoted include micro-deformation of the tissue, epithelial migration, and improved blood flow. These factors contribute to increasing the development of granulation tissue at the tissue site, which results in new tissue growth. While the discussion of providing reduced pressure tissue treatment often refers to "delivering" reduced pressure to the tissue site, it should be apparent to a person of ordinary skill in the art that delivery of reduced pressure typically involves creating a pressure differential between the reduced pressure source 108 and the wound 102. The pressure differential (with a lower pressure at the reduced pressure source 108 than at the wound 102) creates an initial fluid flow from the wound 102 toward the reduced pressure source 108. Once the pressure at the wound 102 nears or equals that of the pressure at the reduced pressure source 108, the reduced pressure may be maintained at the tissue site due to the fluid connection with the reduced pressure source 108 and the sealing function of the drape 132.

[0045] As new tissue forms under the influence of reduced pressure, the new tissue is permitted to grow into the scaffold 140. The material chosen for the scaffold 140 preferably supports and encourages new tissue growth. Since the scaffold 140 will remain at the tissue site following the administration of reduced pressure tissue treatment, it is preferred that new tissue penetrates the scaffold as much as possible. It has been observed that under the influence of reduced pressure, new tissue may penetrate up to 1 mm (thickness) of the scaffold 140 in a period of two days. Since the thickness of the scaffold 140 in some embodiments may only be about 1 to 4 mm, it may be desired to remove the distribution manifold 130 and the release layer 150 of the reduced pressure dressing 110 and replace the layers with a new dressing containing a new distribution manifold 130, a new release layer 150, and additional scaffold material. In other words, a new scaffold 140 may be placed on top of the old scaffold 140 following removal of the distribution manifold 130 and the release layer 150. By

removing only a portion of the reduced pressure dressing 110 and leaving the scaffold 140, it is possible to incrementally add new tissue growth to the wound 102 as new scaffolds 140 are stacked upon previously inserted scaffolds 140 that are already permeated with new tissue growth.

[0046] During the application of reduced pressure, the release material 150 preferably minimizes or prevents contact between the distribution manifold 130 and the scaffold 140 to hinder the growth of new tissue from the scaffold 140 through the release layer 150 and into the distribution manifold 130. New tissue growth into the scaffold 140 is hindered from further growth into the distribution manifold 130 by this separation and by the inherent properties of the release layer 150 as described above. While tissue growth into the distribution manifold 130 may still occur, the growth is minimized, which lessens pain to the patient upon removal of the distribution manifold 130.

[0047] Following application of reduced pressure for a selected period of time, the release material 150 may be hydrated by soaking the reduced pressure dressing 110 with water, saline solution, or other fluids. Alternatively, the reduced pressure dressing 110 may be allowed to sit until bodily fluids from the tissue site hydrate the release layer 150. If the release layer 150 is a hydrogel-forming material, the release layer 150 transforms into a gel-like state and typically expands as it hydrates. This allows for easier removal of the distribution manifold 130 from the scaffold 140. Any hydrogel-forming material (or hydrogel) that remains following removal of the manifold 130 may be manually removed or dissolved by the introduction of additional fluids. Alternatively, if the release layer 150 is a water-soluble polymer, it will be dissolved as it absorbs water or other fluids, thus releasing the distribution manifold 130 from the scaffold 140.

[0048] Referring to FIG. 4A, a method 811 of promoting tissue growth at a tissue site according to an embodiment of the present invention is illustrated. The method 811 includes positioning a multi-layer reduced pressure delivery apparatus in contact with the tissue site at 815. The reduced pressure delivery apparatus includes a scaffold, a release material, and a manifold. At 819, the apparatus is oriented such that the scaffold contacts the tissue site. A reduced pressure is applied to the tissue site through the manifold and the scaffold at 823.

[0049] Referring to FIG. 4B, a method 851 of promoting new tissue growth at a tissue site according to an embodiment of the present invention is illustrated. The method 851 includes at 855 positioning a scaffold in contact with the tissue site, a release material in contact with the scaffold, and a manifold in contact with the release material. At 859, new tissue growth is stimulated at the tissue site by applying a reduced pressure to the tissue site through the manifold and the scaffold.

[0050] Referring to FIG. 5, a tissue growth kit 911 for promoting new tissue growth at a tissue site according to an embodiment of the present invention includes a scaffold 913, a release material 915, and a distribution manifold 917. The scaffold 913 includes a first and second side, the first side of the scaffold 913 being adapted to contact the tissue site. The scaffold 913 is similar to the scaffold 140 described previously with reference to FIGs. 1-3. The release material 915 is adapted to contact the second side of the scaffold 913 and is similar to the release layer 150 described previously with reference to FIGs. 1-3. The distribution manifold 917 is adapted to contact the release material 915 to distribute a reduced pressure to the tissue site through the scaffold 913. The distribution manifold 917 is similar to the manifold 130 described previously with reference to FIGs. 1-3. The tissue growth kit 911 may further include a container 921 for housing the scaffold 913, release material 915, and distribution manifold 917 prior to use of the components. The container 921 may be a flexible bag, a box, or any other container suitable for storing the scaffold 913, release material 915, and distribution manifold 917.

[0051] While the multi-layer reduced pressure delivery apparatus disclosed herein is used in conjunction with a reduced pressure delivery source to provide reduced pressure tissue treatment to a tissue site, the reduced pressure dressing could also serve as an advanced tissue dressing alone in the absence of reduced pressure application. The same materials, relative positioning, and connectivity between layers may be used in the advanced tissue dressing. Similar to the reduced pressure dressing described herein, the advanced tissue dressing may include a first layer to promote and accept growth of new tissue, a third layer to assist in directing fluids away from the tissue site, and a second layer to facilitate removal of the third layer from the first layer at a selected time. The third layer of the advanced tissue dressing, instead of having a "manifold", may be considered to include a fluid reservoir for collecting and holding fluids exuded by the wound. The materials described herein as being suitable

distribution manifold materials are similarly suitable materials for the reservoir of the third layer. The only requirement of the reservoir is that the reservoir should be made from a material that is capable of storing fluids produced by or present at the tissue site.

[0052] As discussed above, normal endogenous levels of MMPs are essential for tissue remodeling during the wound healing process. However, in excess, they continually break down the new tissue that is formed. This leads to a wound that either does not heal quickly or becomes "stalled." Excess levels of ROS and MMPs create a sustained state of inflammation thereby preventing the progression of normal wound healing. Accordingly, in certain aspects, the invention provides methods for promoting wound healing by providing a biologically active composition comprising a lipoic acid derivative in an amount effective to reduce the level of ROS and/or reduce inflammation at the wound site and in surrounding tissue.

[0053] The term "lipoic acid derivative" refers to molecules structurally related to alpha-lipoic acid, or a salt thereof such as sodium lipoate, that function as an antioxidant *in vivo*. A wide array of lipoic acid derivatives are known in the art and may be used according to the invention. For example, U.S. Patent No. 6,887,891 (incorporated herein by reference in its entirety) details a number of lipoic acid derivatives any of which may be used in accordance with the invention. Certain generalized structures for lipoic acid derivative molecules are depicted in FIG. 6A-B. For example, a lipoic acid derivative may have a structure according to FIG. 6A wherein n_1 and n_2 are, independently, C_1-C_{10} alkyl; and R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid. Likewise, a lipoic acid derivative may have a structure according to FIG. 6B wherein n_1 and n_2 are, independently, C_1-C_{10} alkyl; R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid; and each of the R_2 positions are, independently, H, C_1-C_{10} alkyl or C_6-C_{14} aryl. Salts of alpha-lipoic acid with inorganic cations such as sodium, alkyl ammonium cations, and other pharmaceutically acceptable cations may be used according to the invention. Additionally, a number of esters and thioesters of alpha-lipoic acid can function as pro-drugs, undergoing hydrolysis to alpha-lipoic acid and dihydrolipoic acid *in vivo*.

[0054] Compositions containing alpha-lipoic acid or the pharmaceutically acceptable salt or derivative thereof may be suitable for local or systemic, oral or parenteral administration. The examples of the administration of alpha-lipoic acid include a formulation comprising of 0.001% to 10% w/v, 0.1% to 10%, or 1% to 5% w/v lipoic acid derivative or

salt thereof, in an acceptable carrier. Suitable carriers include, but are not limited to: hydrogels containing cellulose derivatives, including hydroxyethyl cellulose, hydroxymethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose and mixtures thereof; and hydrogels containing polyacrylic acid (Carbopols) as well as gelatin. The above carriers may include alginate (as a thickener or stimulant), preservatives such as benzyl alcohol, buffers to control pH such as disodium hydrogen phosphate/sodium dihydrogen phosphate, agents to adjust osmolarity such as sodium chloride, and stabilizers such as EDTA. Biologically active compositions may, in some embodiments, one or more additional active agents.

[0055] In certain aspects, topical application of antioxidants (*e.g.,* a lipoic acid derivative) to the wound 102 is used to reduce ROS levels and to facilitate the normal healing process of a chronic wound. Other antioxidants for application in wound healing include ascorbic acid, fatty (linolenic, linoleic, and oleic) acids, and N-acetyl cysteine and such antioxidants may additionally be used in compositions disclosed herein. As demonstrated herein, alpha-lipoic acid and its derivatives are potent antioxidants. Major biological effects of alpha-lipoic acid, for example, include normalizing blood sugar levels, improving nerve blood flow, reducing oxidative stress, alleviating diabetic neuropathy, and protecting membranes. Other advantages of lipoic acid molecules over other antioxidants include high antioxidant activity, the ability to scavenge free radicals in both water and fatty tissues, stability to gamma sterilization, and prolonged shelf-life, which is particularly important for medical device applications. Limited solubility in water and moderate hydrophobicity of alpha-lipoic acid are preferable for formulations that require graduate sustained release of antioxidants. These properties combined with low cost of derivatives such as alpha-lipoic acid make it a preferable solution for treatment of chronic wounds in general, and for incorporation into wound dressing such as the scaffold 140 of the wound dressing 110 described above.

[0056] Although alpha-lipoic acid is stable to gamma-sterilization and temperatures up to 60°C, it may undergo partial decomposition in some storage conditions, like high humidity and low temperature, which is accompanied by an unpleasant odor due to its sulfur content. However, conversion of alpha-lipoic acid into a salt derivative, such as sodium lipoate, or the use of polymer barriers in the wound dressing 110 mitigates the odor issues. For example, a lipoic acid derivative may be converted to a salt at a pH of about 6 to about 8. Within this pH range lipoic acid derivatives, such as alpha-lipoic acid, can be efficiently converted to a salt to

reduce odor without significant loss of antioxidant activity. Thus, in certain aspects, the invention provides compositions having reduced odor properties comprising a pharmaceutically acceptable salt of a lipoic acid derivative (*e.g.,* sodium lipoate).

[0057] When the alpha-lipoic acid is converted enzymatically into dihydrolipoic acid, the dihydrolipoic acid is more potent than alpha-lipoic acid at neutralizing superoxide radicals, hydroperoxy radicals, hydroxyl radicals, and other major ROS and the antioxidant activity of the lipoic acid actually increases in the cells. Application of stable molecule of alpha-lipoic acid, which converts in the body into extremely potent antioxidant is highly advantageous from the handling and shelf-life perspectives. Thus, in certain aspects, a lipoic acid derivative for use according to the invention may be a lipoic acid prodrug that is converted into an active antioxidant *in vivo*.

[0058] Excessive MMP activity at a tissue site can also be addressed by providing a biologically active composition comprising a sacrificial proteolytic enzyme substrate, such as protein, protein hydrolysate, or combinations thereof. For example, a sacrificial proteolytic enzyme substrate can comprise keratin, collagen, elastin, gelatin, casein, albumin, fibrinogen, fibronectin, soy protein, wheat protein, corn protein, milk proteins and/or hydrolysates thereof (*see, e.g.,* U.S. Patent No. 6,500,443, incorporated herein by reference). In certain embodiments, proteins for use as sacrificial substrates are hydrolyzed or partially hydrolyzed by treatment with a strong acid or base. Such treatment can fragment the subject proteins and generate more accessible peptide sequence to bind to proteolytic enzymes.

[0059] The most prevalent MMPs in chronic wounds are the gellatinase proteases, MMP-2 and MMP-9 that more readily target the hydrolyzed or denatured form of collagen known as "gelatin." Thus, in certain aspects, a biologically active composition for use as described here further comprises a collagen, such as a hydrolyzed collagen (*e.g.,* gelatin). Gelatin can be processed from a variety of sources including, but not limited to, bovine skin, pig skin and bone material. Depending on the hydrolysis methods employed in manufacture, the gelatin may be defined as a type A or type B gelatin. One advantage of using a gelatin rather than, or in addition to, collagen is that gelatin includes exposed peptide sequences that serve as signals for protease binding. Accessibility of signaling sequences in the native collagen molecule is diminished due to triple-helix structure of native collagen molecule, where polypeptide chains are bound with strong hydrogen bonds. Thus, in certain aspects, a

biologically active composition is defined as not comprising collagen. In the case of gelatin, on the other hand, signaling sequences are readily exposed to proteases making it more efficient as a sacrificial substrate.

[0060] A primary constraint against using gelatin in wound dressings is insufficient mechanical integrity and inability to maintain dressing shape in wound environment as is possible with natural collagen. However, if gelatin is applied as a coating onto another porous material, such as polyurethane foam, which will provide structural support, such dressing with gelatin can be an excellent choice as an MMP sacrificial substrate. Gelatin for use in biologically active compositions will, nonetheless, need to comprise sufficient gel strength to form an adherent layer on a porous material without causing the material to become overly stiff. Accordingly, gelatin for use in biologically active compositions can comprise a bloom value of between about 150-300 g, between about 200-250 g or about 225 g.

[0061] Additionally, gelatin is an excellent oxygen barrier, which is important for stability of molecules that could be incorporated in the dressings, such as antioxidants and oxygen sensitive proteins and peptides. Thus, the scaffold 140 may be a polyurethane foam as described above that is coated with gelatin to provide the reduced pressure dressing 110 with a sacrificial substrate for MMPs. Biologically active compositions may, for example, comprise 0.1% to 25%, 1% to 10% or about 6%, 8%, 10%, 15% or 20% w/w gelatin.

[0062] In certain aspects, a biologically active composition, such as a composition coated on a porous material is sterilized by irradiation. A skilled worker will recognize that such irradiation can alter the amount of cross-linking within proteins in the composition. Thus, in cases where composition comprises a sacrificial proteolytic enzyme substrate that is a protein, such as gelatin, the amount of irradiation may be adjusted not only to achieve sterilization but also to achieve a desired level of protein cross-linking. For example, a gelatin with a relatively low bloom value can be used in a coating and then subjected to irradiation to increase the effective bloom value of the gelatin coating by further cross-linking the protein. In certain aspects, biologically active compositions and/or wound dressings according to the invention are subjected to gamma irradiation, such as between about 10-80 Gy, about 20-60 Gy or about 30-50 Gy of radiation.

[0063] Biologically active compositions may be formulated as a solution, a spray, a cream, a gel or coating provided on a scaffold. Such compositions may be formulated for

time-controlled release of the lipoic acid derivative. For example, the formulation may be formulated such that the lipoic acid derivative is released over a period of about 12 hours, 24 hours, 2 days, 3 days 4 days or 1 or more weeks.

[0064] In certain aspects, a biologically active composition is coated onto the surface and into the pores of a scaffold 140, as detailed above. Methods for coating such a scaffold may, for example, comprise the steps of (i) saturating a porous substrate material with a solution comprising the components of a biologically active composition; and (ii) drying the porous substrate thereby producing a wound healing scaffold coated with a biologically active composition. For example, the coating solution may comprise a lipoic acid derivative (*e.g.,* alpha-lipoic acid or sodium lipoate) and gelatin. In certain aspects, the substrate material is dried such that the resulting wound healing scaffold comprises a moisture content of less than about 5%.

[0065] Biologically active compositions disclosed herein may further comprise other biologically active molecules such as antimicrobial agents, growth factors, proteinase inhibitors, chelating agent or preservatives. For example, in certain aspects the composition additionally comprises a metal chelating agent capable of reducing MMP activity, such as EDTA. Antimicrobial agents may also be used in compositions according to the invention. For example, the composition may include antibiotics, antifungal agents or more general antimicrobials. Antimicrobial compounds compatible with lipoic acid formulation include, but are not limited to, non-ionic silver, polyhexamethylene biguanide, chlorhexidine, benzalconium chloride, triclosan and others.

[0066] As described below, the combination of a lipoic acid derivative and gelatin promotes healing or prophylaxis of chronic ulcers by regulating level of ROS and matrix metalloproteinases (MMP's) at the ulcer site. The balance between reactive oxygen species, proteolytic enzymes and their inhibitors is critical to the persistence and healing of chronic ulcers, and that the alpha-lipoic acid corrects this balance in chronic ulcers. Alpha-lipoic acid, for example, inhibits the influx of inflammatory cells to a wound site by inhibiting the transcription of genes for adhesion molecules such as ICAM-1 and other adhesion molecules on inflammatory cells and endothelial cells. The alpha-lipoic acid inhibits the activation of nuclear transcription factors such as NF-κB, which controls the transcription of the MMP-9 gene, adhesion molecule genes such as ICAM-1, and inflammatory mediator genes such as

TNF-alpha. Finally, alpha-lipoic acid can interfere with the inflammatory mediators such as leukotrienes.

[0067] Biologically active compositions may be infused within, or coated on, the scaffold 140. For example, the composition of alpha-lipoic acid may be coated on a woven, non-woven, or knitted fabric material. Alternatively, the alpha-lipoic acid may be dispersed within a bioresorbable polymeric film, sponge, or foam for sustained release at the wound 102. The alpha-lipoic acid may also be coated with gelatin on a polyurethane reticulated foam as described in the following Example.

[0068] The formulation of lipoic acid and gelatin applied as a coating on the open-cell reticulated polyurethane foam pads provides unique combination of effects and is highly effective for healing of chronic wounds. The formulation can be used in combination with negative pressure wound therapy, which is known to be highly effective in stimulating growth of granulation tissue, reducing infection and maintaining proper moisture balance in the wound. Addition gelatin and lipoic acid and EDTA to the dressing specifically addresses healing of chronic wounds removing barriers to normal healing such as abnormally high levels of ROS and MMPs. It should be noted that MMP aspect of wound healing is addressed by formulations described in herein from several perspectives, *i.e.,* the reduction of ROS levels to affect recruitment of MMPs, the addition of EDTA to prevent MMP from activation, and gelatin to service as sacrificial substrate for MMPs preserving newly formed granulation tissue.

[0069] Examples.

[0070] The following examples are included to demonstrate certain embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and

modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

[0071] Example 1

[0072] Polyurethane open-cell reticulated foam pads were selected as the scaffold 140 and were immersed in a solution containing 1.5 wt % of alpha-lipoic acid and 4.5 wt % 225-bloom beef gelatin (and, where applicable, 0.3 % EDTA). Gelatin was used as a biocompatible binding agent with good oxygen barrier and sustained release properties for alpha-lipoic acid as well as for its ability to act as a sacrificial substrate for surrounding gelatinases. Alpha-lipoic acid was pre-dissolved in ethanol and then mixed into the final solution. The foam pads were immersed for a sufficient amount of time to coat the pathways formed within the open-cell reticulated foam as described above with respect to the scaffold 140. After immersion, the foam pads were withdrawn, compressed to remove excess solution, and dried to a constant weight. In some cases, sodium benzoate was added to the formulation as a preservative. Dried foams comprised, by weight, 2% alpha-lipoic acid, 6% gelatin and, where applicable, 0.4% EDTA.

[0073] A National Diagnostics Hydrogen Peroxide Assay Kit was used to evaluate the antioxidant properties of foam pads and the formulated coated foam pads containing alpha-lipoic acid. Foam pads coated only with gelatin were used as controls. FIG. 7 is a graph showing the percentage of hydrogen peroxide reduction due to reaction with alpha-lipoic acid. An MMP-9 Colorimetric Drug Discovery Kit (Biomol) was used to evaluate the MMP inhibiting/inactivating ability of the formulated foam pads containing alpha-lipoic acid/gelatin (ALA) and gelatin alone (GF GEL). The controls were uncoated foam pads and known potent MMP inactivating drug, NNGH ($C_{13}H_{20}N_2O_5S$, available from Enzo® Life Sciences). FIG. 8 is a graph showing that gelatin-coated foam pads inhibit MMP activity, but the combination of gelatin and ALA along with the EDTA (described in Example 2) are much more potent than gelatin alone. FIG. 9 is a graph showing the release of alpha-lipoic acid from the coating on the foam pads. The coating delivers approximately 70% of the total alpha-lipoic acid within the first day, while the remaining alpha-lipoic acid is released during the next 2-3 days.

[0074] Example 2

[0075] Chelating agents like ethlenediaminetetraacetic acid (EDTA) were added to the dipping solution described in Example 1. The addition of EDTA to wound dressings prevents MMP from activation chelating zinc ions essential for activation of pro-MMPs.

[0076] Example 3

[0077] A solution of sodium hydroxide can be added to the dipping solution described in Examples 1-2 to convert lipoic acid into sodium lipoate. The pH of resulting solution should be in the range between 6 and 8. The conversion of lipoic acid into sodium lipoate eliminates the risk of development of sulphur odor in the coated foams.

[0078] Example 4

[0079] Coated polyurethane foam (GranuFoam®) scaffolds described above in Examples 1-2 were further assayed for their ability to reduce MMP activity as compared to non-coated collagen based scaffold such as the Biostep™ and Promogran™ products. The results from two separate experiments are presented below in Tables 1 and 2 and demonstrate that the coated scaffolds reduced MMP activity similarly to collagen scaffolds, even though the coated scaffolds only comprised 10% by weight biologically active layer.

[0080] Table 1:

Dressing treatment	% MMP-9 activity reduction*	Standard deviation
NNGH	90.2	1.2
Foam	34.5	9.6
Foam + gelatin	42.2	8.4
Foam + gelatin + ALA + EDTA	65.8	0.0
Promogran™	68.7	0.5
Biostep™	82.2	1.8

* All values indicate the amount of MMP-9 activity reduction as compared to control samples with no MMP-9 inhibitor activity. ALA indicates alpha-lipoic acid coating.

[0081] Table 2:

Dressing treatment	% MMP-9 activity reduction*	Standard deviation
NNGH	103.8 %	2.1
Foam	27.1 %	0.2
Foam + gelatin	72.6 %	21.8
Foam + gelatin + EDTA	54.5 %	3.5
Foam + gelatin + ALA + EDTA	90.4 %	1.9
Promogran™	100.8 %	4.5
Biostep™	104.6 %	3.0

* All values indicate the amount of MMP-9 activity reduction as compared to control samples with no MMP-9 inhibitor activity. ALA indicates alpha-lipoic acid coating.

[0082] Example 5

[0083] The radiation stability of alpha-lipoic acid coated scaffolds described above were assessed by measuring the effectiveness of scaffold at decreasing ROS after gamma irradiation. Briefly, irradiated and control scaffolds were treated with 20 μM H_2O_2. Peroxide concentration was then measured using a TBR4100 with HPO-100 sensor (available from World Precision Instruments) at 2 hours or 24 hours after treatment. The results of these studies are summarized in Table 3. Results represent the average peroxide reduction measured

in 10 replicates. As shown, the alpha-lipoic acid coating remained highly active (*i.e.,* as an antioxidant) even after extensive irradiation.

[0084] Table 3:

Dressing irradiation treatment	ROS reduction 2 hr.	ROS reduction 24 Hours
Foam alone control (0Gy)	19 %	31 %
30 Gy	45 %	83 %
40 Gy	55 %	87 %
50 Gy	59 %	86 %
60 Gy	59 %	85 %

[0085] While the systems and methods of the present invention have been described with reference to tissue growth and healing in human patients, it should be recognized that these systems and methods for applying reduced pressure tissue treatment can be used in any living organism in which it is desired to promote tissue growth or healing. Similarly, the systems and methods of the present invention may be applied to any tissue, including without limitation bone tissue, adipose tissue, muscle tissue, dermal tissue, vascular tissue, connective tissue, cartilage, tendons, or ligaments. While the healing of tissue may be one focus of applying reduced pressure tissue treatment as described herein, the application of reduced pressure tissue treatment may also be used to generate tissue growth in tissues that are not diseased, defective, or damaged. For example, it may be desired to apply reduced pressure tissue treatment to grow additional tissue at a tissue site that can then be harvested. The harvested tissue may be transplanted to another tissue site to replace diseased or damaged tissue, or alternatively the harvested tissue may be transplanted to another patient.

[0086] Although the present invention and its advantages have been disclosed in the context of certain illustrative, non-limiting embodiments, it should be understood that various changes, substitutions, permutations, and alterations can be made without departing from the scope of the invention as defined by the appended claims.

CLAIMS

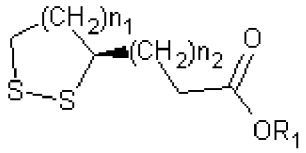
We claim:

Claim 1. A wound dressing for applying treatment to a tissue site comprising:

a porous polyurethane material having a portion to contact the tissue site; and

a composition comprising a lipoic acid derivative and a sacrificial proteolytic enzyme substrate deposited on the portion of the porous polyurethane material.

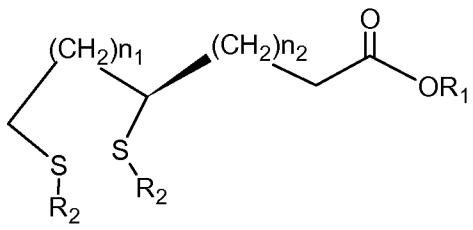
Claim 2. The wound dressing of claim 1, wherein the lipoic acid derivative comprises the structure:



wherein n1 and n2 are, independently, C_1-C_{10} alkyl; and

R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid.

Claim 3. The wound dressing of claim 1, wherein the lipoic acid derivative is a dihydrolipoic acid comprising the structure:



wherein n1 and n2 are, independently, C_1-C_{10} alkyl;

R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid; and

R_2 is H, C_1-C_{10} alkyl or C_6-C_{14} aryl.

Claim 4. The wound dressing of any preceding claim, wherein the lipoic acid derivative is provided as a pharmaceutically acceptable salt.

Claim 5. The wound dressing of any preceding claim, wherein the lipoic acid derivative is alpha-lipoic acid or a pharmaceutically acceptable salt of alpha-lipoic acid.

Claim 6. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises keratin or hydrolysates thereof.

Claim 7. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises collagen or hydrolysates thereof.

Claim 8. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises elastin or hydrolysates thereof.

Claim 9. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises gelatin or hydrolysates thereof.

Claim 10. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises casein or hydrolysates thereof.

Claim 11. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises albumin or hydrolysates thereof.

Claim 12. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises fibrinogen or hydrolysates thereof.

Claim 13. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises fibronectin or hydrolysates thereof.

Claim 14. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises soy protein or hydrolysates thereof.

Claim 15. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises wheat protein or hydrolysates thereof.

Claim 16. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises corn protein or hydrolysates thereof.

Claim 17. The wound dressing of any preceding claim, wherein the sacrificial proteolytic enzyme substrate comprises milk proteins or hydrolysates thereof.

Claim 18. The wound dressing of any one of claims 1 to 6 or 8 to 17, wherein the sacrificial proteolytic enzyme substrate does not comprise collagen.

Claim 19. The wound dressing of claim 18, wherein the sacrificial proteolytic enzyme substrate comprises gelatin.

Claim 20. The wound dressing of any preceding claim, wherein the wound dressing comprises 0.01% to 10% or more preferably 0.1% to 5% w/w lipoic acid derivative.

Claim 21. The wound dressing of any preceding claim, wherein the biologically active composition comprises at least 4% w/w of a sacrificial proteolytic enzyme substrate.

Claim 22. The wound dressing of any one of claims 1 to 20, wherein the biologically active composition comprises at least 6% w/w of a sacrificial proteolytic enzyme substrate.

Claim 23. The wound dressing of any one of claims 1 to 20, wherein the biologically active composition comprises at least 8% w/w of a sacrificial proteolytic enzyme substrate.

Claim 24. The wound dressing of any one of claims 1 to 20, wherein the biologically active composition comprises at least 10% w/w of a sacrificial proteolytic enzyme substrate.

Claim 25. The wound dressing of any one of claims 1 to 20, wherein the biologically active composition comprises at least 15% w/w of a sacrificial proteolytic enzyme substrate.

Claim 26. The wound dressing of any one of claims 1 to 20, wherein the biologically active composition comprises at least 20% w/w of a sacrificial proteolytic enzyme substrate.

Claim 27. The wound dressing of any preceding claim, wherein the biologically active composition further comprises an antimicrobial agent.

Claim 28. The wound dressing of any preceding claim, wherein the biologically active composition further comprises a growth factor.

Claim 29. The wound dressing of any preceding claim, wherein the biologically active composition further comprises a proteinase inhibitor.

Claim 30. The wound dressing of any preceding claim, wherein the biologically active composition further comprises a chelating agent.

Claim 31. The wound dressing of any preceding claim, wherein the biologically active composition further comprises a preservative.

Claim 32. The wound dressing of claim 27 or any claim appendent thereto, wherein the antimicrobial agent is non-ionic silver.

Claim 33. The wound dressing of claim 27 or any claim appendent thereto, wherein the antimicrobial agent is polyhexamethylene biguanide.

Claim 34. The wound dressing of claim 27 or any claim appendent thereto, wherein the antimicrobial agent is chlorhexidine.

Claim 35. The wound dressing of claim 27 or any claim appendent thereto, wherein the antimicrobial agent is benzalconium chloride.

Claim 36. The wound dressing of claim 27 or any claim appendent thereto, wherein the antimicrobial agent is triclosan.

Claim 37. The wound dressing of claim 30 or any claim appendent thereto, wherein the chelating agent is ethylenediaminetetraacetic acid.

Claim 38. The wound dressing of any preceding claim, wherein the porous polyurethane material is an open-cell foam comprising a plurality of passages interconnecting pores within the material.

Claim 39. A wound dressing for applying a reduced pressure treatment to a tissue site comprising:

a porous polyurethane material having a plurality of passages to distribute reduced pressure to the tissue site; and

a composition comprising a lipoic acid derivative and a sacrificial proteolytic enzyme substrate deposited on the porous polyurethane material.

Claim 40. A reduced pressure therapy system comprising:

a scaffold having a plurality of passages to distribute a reduced pressure to a tissue, the scaffold having exterior surfaces, the scaffold further having interior surfaces along the plurality of passages;

a biologically active composition uniformly covering the exterior surfaces of the scaffold and the interior surfaces of the scaffold along the passages wherein the biologically active composition comprises a lipoic acid derivative;

a drape adapted to be positioned over the scaffold to maintain a sealable space over the wound; and

a vacuum source in fluid communication with the sealable space to deliver the reduced pressure to the sealable space.

Claim 41. The system of claim 40, wherein the biologically active composition allows the lipoic acid derivative to be released to the tissue.

Claim 42. The system of claim 40 or claim 41, wherein the reduced pressure applied to the scaffold causes an increased area of contact between the scaffold and the tissue, thereby increasing exposure of the tissue to the biologically active composition.

Claim 43. The system of claim 42, wherein the inflammatory activity in the tissue is reduced by causing the increased area of contact.

Claim 44. The system of claim 42 or claim 43, wherein the reduced pressure compresses the foam pad against the tissue to form the increased area of contact.

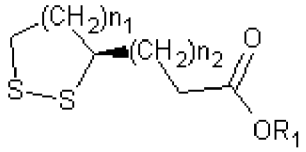
Claim 45. The system of any one of claims 40 to 44, wherein inflammatory activity in the tissue is reduced by removal of body-liquid from the tissue into the passages and by the exposure of the body-liquid in the passage to the biologically active composition.

Claim 46. The system of any one of claims 40 to 45, wherein the biologically active composition releases the lipoic acid derivative in an aqueous environment.

Claim 47. The system of any one of claims 40 to 46, wherein the scaffold is an open-cell foam and the plurality of passages are interconnected pores within the scaffold.

Claim 48. The system of any one of claims 40 to 47, further comprising a manifold adapted to provide reduced pressure to the scaffold and the tissue.

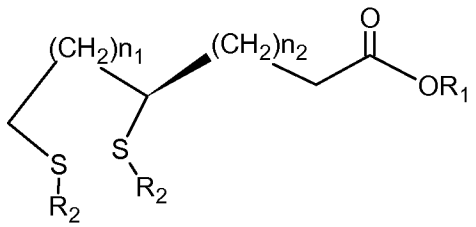
Claim 49. The system of any one of claims 40 to 48, wherein the lipoic acid derivative comprises the structure:



wherein n1 and n2 are, independently, C_1-C_{10} alkyl; and

R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid.

Claim 50. The system of any one of claims 40 to 48, wherein the lipoic acid derivative is a dihydrolipoic acid comprising the structure:



wherein n1 and n2 are, independently, C_1-C_{10} alkyl;

R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid; and

R_2 is H, C_1-C_{10} alkyl or C_6-C_{14} aryl.

Claim 51. The system of any one of claims 40 to 50, wherein the biologically active composition further comprises a sacrificial proteolytic enzyme substrate.

Claim 52. The system of claim 46, wherein the sacrificial proteolytic enzyme substrate comprises gelatin.

Claim 53. The system of any one of claims 40 to 52, wherein the lipoic acid derivative is alpha-lipoic acid or sodium lipoate.

Claim 54. The system of any one of claims 40 to 53, wherein the biologically active composition comprises 0.01% to 10% or more preferably 0.1% to 5% w/w lipoic acid derivative.

Claim 55. The system of claim 51 or any claim appendent thereto, wherein the biologically active composition comprises at least 4% w/w of a sacrificial proteolytic enzyme substrate.

Claim 56. The system of claim 51 or any claim appendent thereto, wherein the biologically active composition comprises at least 6% w/w of a sacrificial proteolytic enzyme substrate.

Claim 57. The system of claim 51 or any claim appendent thereto, wherein the biologically active composition comprises at least 8% w/w of a sacrificial proteolytic enzyme substrate.

Claim 58. The system of claim 51 or any claim appendent thereto, wherein the biologically active composition comprises at least 10% w/w of a sacrificial proteolytic enzyme substrate.

Claim 59. The system of claim 51 or any claim appendent thereto, wherein the biologically active composition comprises at least 15% w/w of a sacrificial proteolytic enzyme substrate.

Claim 60. The system of claim 51 or any claim appendent thereto, wherein the biologically active composition comprises at least 20% w/w of a sacrificial proteolytic enzyme substrate.

Claim 61. The system of any one of claims 40 to 60, wherein the biologically active composition further comprises an antimicrobial agent.

Claim 62. The system of any one of claims 40 to 61, wherein the biologically active composition further comprises a growth factor.

Claim 63. The system of any one of claims 40 to 62, wherein the biologically active composition further comprises a proteinase inhibitor.

Claim 64. The system of any one of claims 40 to 63, wherein the biologically active composition further comprises a chelating agent.

Claim 65. The system of any one of claims 40 to 64, wherein the biologically active composition further comprises a preservative.

Claim 66. The system of any one of claims 40 to 65, wherein the antimicrobial agent is non-ionic silver.

Claim 67. The system of any one of claims 40 to 66, wherein the antimicrobial agent is polyhexamethylene biguanide.

Claim 68. The system of any one of claims 40 to 67, wherein the antimicrobial agent is chlorhexidine.

Claim 69. The system of any one of claims 40 to 68, wherein the antimicrobial agent is benzalconium chloride.

Claim 70. The system of any one of claims 40 to 69, wherein the antimicrobial agent is triclosan.

Claim 71. The system of claim 64 or any claims appendent thereto, wherein the chelating agent is ethylenediaminetetraacetic acid.

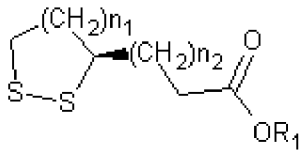
Claim 72. The system of any one of claims 40 to 71, wherein the scaffold is comprised of polyurethan or collagen.

Claim 73. A method for manufacturing a wound healing dressing comprising:

(i) saturating a porous substrate material with a solution comprising a lipoic acid derivative; and

(ii) drying the porous substrate thereby producing a wound healing dressing coated with a biologically active composition comprising a lipoic acid derivative.

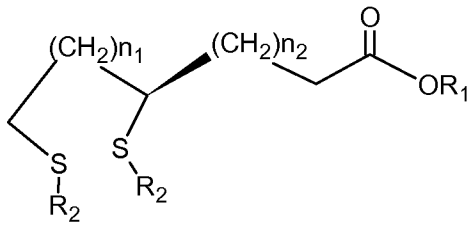
Claim 74. The method of claim 73, wherein the lipoic acid derivative comprises the structure:



wherein n1 and n2 are, independently, C_1-C_{10} alkyl; and

R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid.

Claim 75. The method of claim 73, wherein the lipoic acid derivative is a dihydrolipoic acid comprising the structure:



wherein n1 and n2 are, independently, C_1-C_{10} alkyl;

R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid; and

R_2 is H, C_1-C_{10} alkyl or C_6-C_{14} aryl.

Claim 76. The method of any one of claims 73 to 75, wherein the solution further comprises a sacrificial proteolytic enzyme substrate and wherein biologically active composition comprises a lipoic acid derivative and a sacrificial proteolytic enzyme substrate.

Claim 77. The method of any one of claims 73 to 76, wherein the sacrificial proteolytic enzyme substrate comprises gelatin.

Claim 78. The method of any one of claims 73 to 77, wherein the lipoic acid derivative is alpha-lipoic acid or a pharmaceutically acceptable salt of alpha-lipoic acid.

Claim 79. The method of any one of claims 73 to 78, wherein the solution further comprises sodium hydroxide and wherein the lipoic acid derivative is converted to a sodium salt.

Claim 80. The method of any one of claims 73 to 79, wherein drying the porous substrate comprises, drying the porous substrate to a moisture content of less than 5%.

Claim 81. The method of any one of claims 73 to 80, further comprising sterilizing the porous substrate.

Claim 82. The method of any one of claims 73 to 81, wherein the solution comprises 0.1% to 5% w/v lipoic acid derivative.

Claim 83. The method of claim 76 or any claim appendant thereto, wherein the solution comprises 0.1% to 25% w/v of a sacrificial proteolytic enzyme substrate.

Claim 84. The method of any one of claims 73 to 83, wherein the solution comprises an antimicrobial agent.

Claim 85. The method of any one of claims 73 to 84, wherein the solution comprises a growth factor.

Claim 86. The method of any one of claims 73 to 85, wherein the solution comprises a proteinase inhibitor.

Claim 87. The method of any one of claims 73 to 86, wherein the solution comprises a chelating agent.

Claim 88. The method of any one of claims 73 to 87, wherein the solution comprises a preservative.

Claim 89. The method of any one of claims 73 to 88, wherein the porous substrate material comprises polyurethan or collagen.

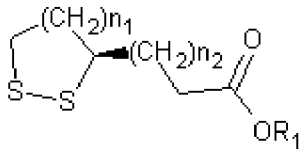
Claim 90. The method of any one of claims 73 to 89, wherein the porous substrate material is flexible.

Claim 91. The method of any one of claims 73 to 90, wherein the porous substrate material is an open-cell foam comprising a plurality of passages interconnecting pores within the substrate.

Claim 92. A method for promoting wound healing comprising contacting a wound site with a biologically active composition comprising a lipoic acid derivative and a sacrificial proteolytic enzyme substrate.

Claim 93. The method of claim 92, wherein the biologically active composition is a solution, a cream or a gel.

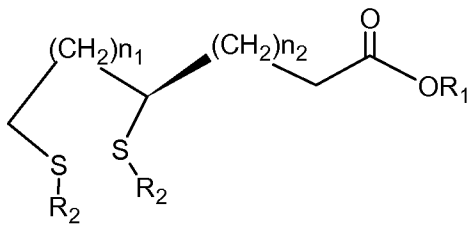
Claim 94. The method of claim 93, wherein the lipoic acid derivative comprises the structure:



wherein n1 and n2 are, independently, C_1-C_{10} alkyl; and

R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid.

Claim 95. The method of claim 93, wherein the lipoic acid derivative is a dihydrolipoic acid comprising the structure:



wherein n1 and n2 are, independently, C_1-C_{10} alkyl;

R_1 is H, C_1-C_{10} alkyl, C_6-C_{14} aryl, an alkyl ammonium or a protonated amino acid; and

R_2 is H, C_1-C_{10} alkyl or C_6-C_{14} aryl.

Claim 96. The method of any one of claims 92 to 95, wherein the lipoic acid derivative is provided as a pharmaceutically acceptable salt.

Claim 97. The method of any one of claims 92 to 96, wherein the lipoic acid derivative is alpha-lipoic acid or sodium lipoate.

Claim 98. The method of any one of claims 92 to 97, wherein the sacrificial proteolytic enzyme substrate comprises gelatin.

Claim 99. The method of any one of claims 92 to 98, wherein the biologically active composition comprises 0.1% to 5% or more preferably 0.01% to 10% w/w lipoic acid derivative.

Claim 100. The method of any one of claims 92 to 99, wherein the biologically active composition comprises 0.1% to 25% w/w of a sacrificial proteolytic enzyme substrate.

Claim 101. The method of any one of claims 92 to 100, wherein the biologically active composition comprises an antimicrobial agent.

Claim 102. The method of any one of claims 92 to 101, wherein the biologically active composition comprises a growth factor.

Claim 103. The method of any one of claims 92 to 102, wherein the biologically active composition comprises a proteinase inhibitor.

Claim 104. The method of any one of claims 92 to 98, wherein the biologically active composition comprises a chelating agent.

Claim 105. The method of any one of claims 92 to 99, wherein the biologically active composition comprises a preservative.

Claim 106. The method of claim 101 or any claim appendent thereto, wherein the antimicrobial agent is non-ionic silver.

Claim 107. The method of claim 101 or any claim appendent thereto, wherein the antimicrobial agent is polyhexamethylene biguanide.

Claim 108. The method of claim 101 or any claim appendent thereto, wherein the antimicrobial agent is chlorhexidine.

Claim 109. The method of claim 101 or any claim appendent thereto, wherein the antimicrobial agent is benzalconium chloride.

Claim 110. The method of claim 101 or any claim appendent thereto, wherein the antimicrobial agent is triclosan.

Claim 111. The method of claim 104 or any claim appendent thereto, wherein the chelating agent is ethylenediaminetetraacetic acid.

Claim 112. The method of any one of claims 92 to 111, wherein the biologically active composition is provided as a coating on a wound dressing.

Claim 113. The method of any one of claims 92 to 112, wherein the wound dressing comprises polyurethan or collagen.

Claim 114. The method of any one of claims 92 to 113, wherein the wound dressing is comprised of a flexible material.

Claim 115. The method of any one of claims 92 to 114, further comprising:

positioning the wound dressing adjacent a wound, the wound dressing having a plurality of passages to distribute a reduced pressure to the wound, the wound dressing having exterior surfaces, the wound dressing further having interior surfaces along the plurality of passages, the wound dressing having biologically active composition covering the exterior surfaces of the wound dressing and the interior surfaces along the passages;

positioning a drape over the foam pad to create a sealable space;

delivering the reduced pressure to the sealable space;

promoting new tissue growth at the wound by exposing the wound to the reduced pressure; and

increasing an area of contact between the wound and the wound dressing to increase the exposure of the wound to the biologically active composition.

Claim 116. The method of claim 115, wherein increasing an area of contact further comprises:

microdeforming the tissue under the influence of the reduced pressure.

Claim 117. The method of claim 115 or claim 116, wherein increasing an area of contact further comprises:

compressing the wound dressing under the influence of the reduced pressure.

Claim 118. The method of claim 115, claim 116 or claim 117 further comprising:

reducing inflammation at the wound by increasing exposure of tissue at the wound to the biologically active composition.

Claim 119. The method of any one of claims 115 to 117 further comprising:

reducing inflammation at the wound by removing body-liquid from the tissue into the passages and by exposing the body-liquid in the passages to the biologically active composition.

Claim 120. A dressing for treating a wound at a tissue site, the dressing comprising:

a scaffold adapted for positioning in fluid communication with the wound, said scaffold being coated with a biologically active composition comprising a lipoic acid derivative and a sacrificial proteolytic enzyme substrate; and

a drape having an adhesive surface for adhering to the tissue site to cover said scaffold when positioned within the wound and form a substantially sealed space when positioned within the wound.

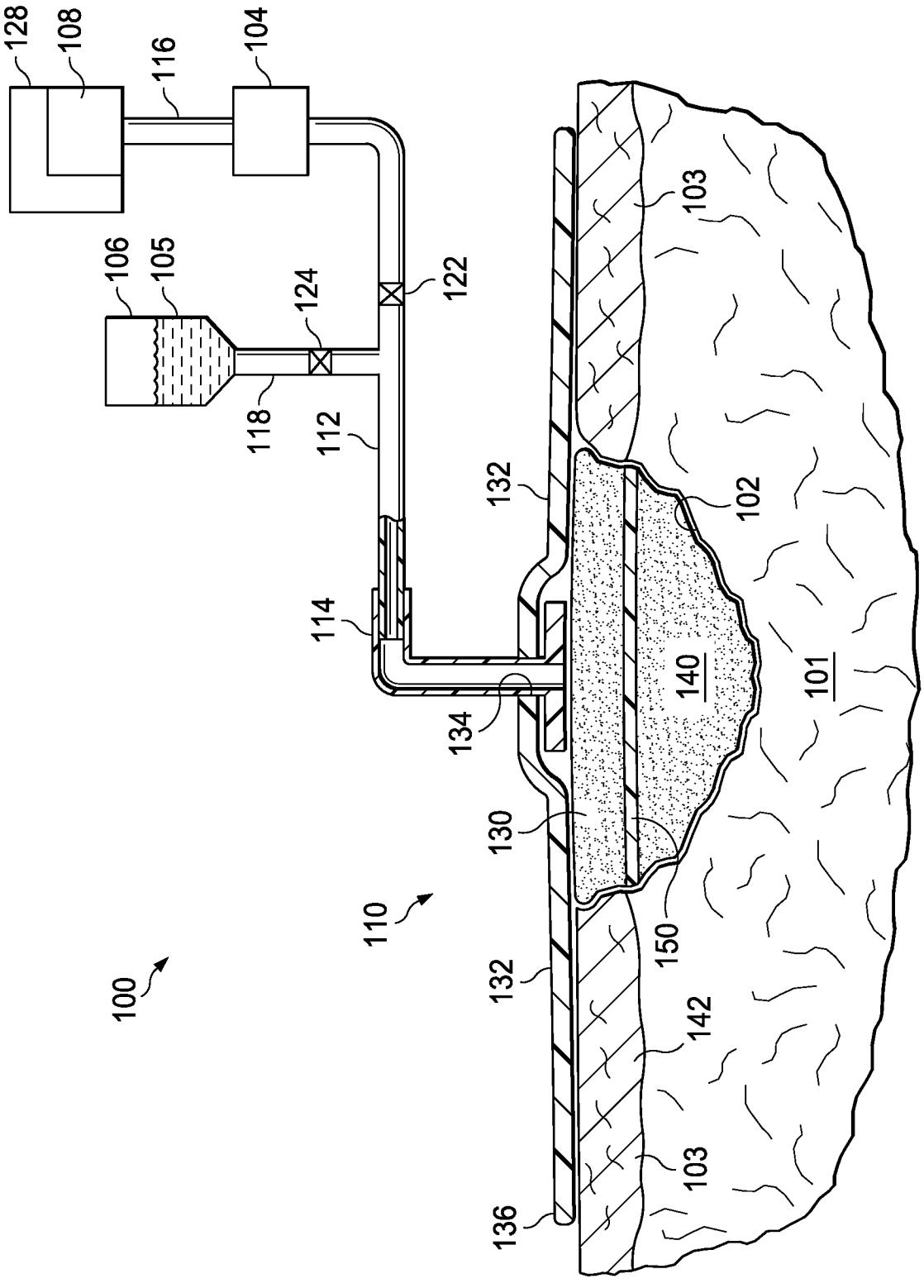

128
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FIG. 1

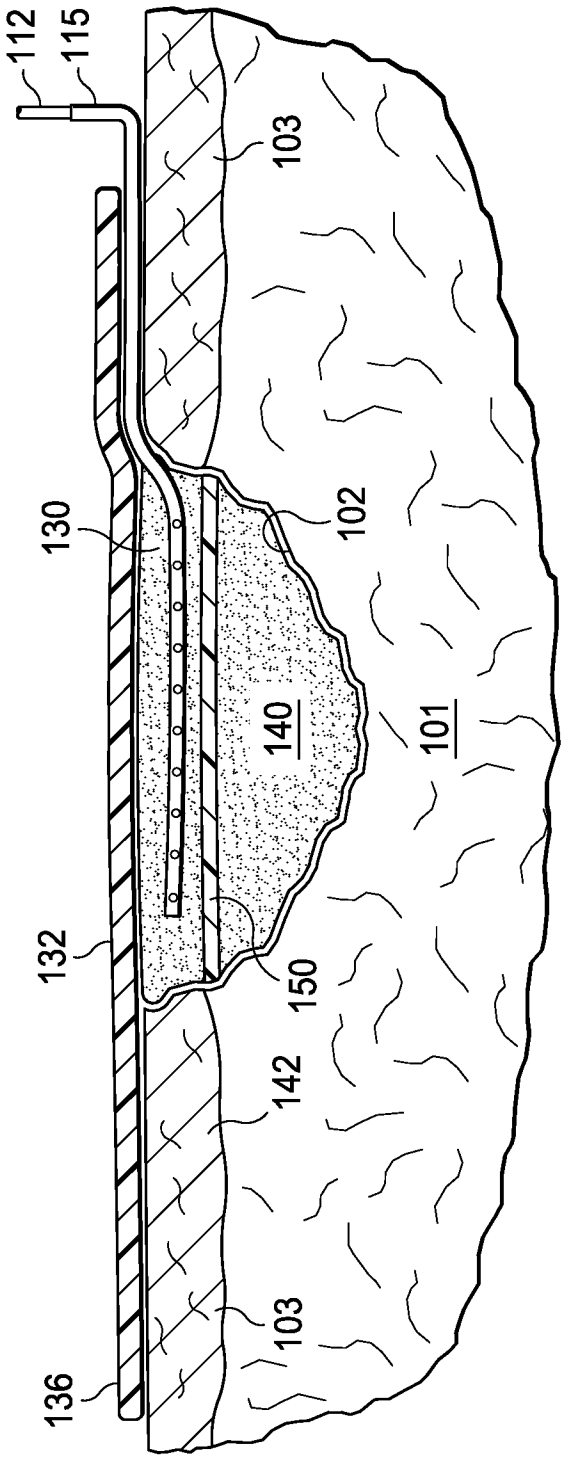
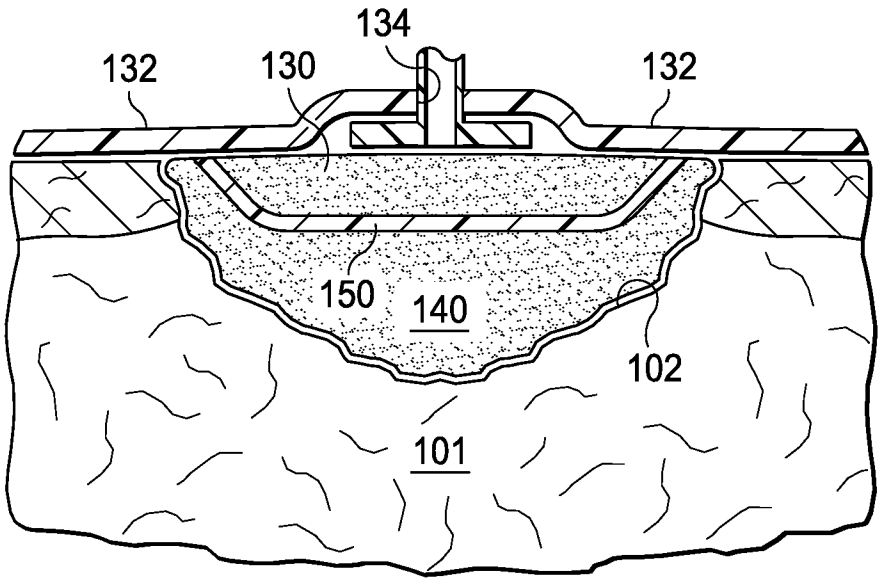


FIG. 2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101

FIG. 3

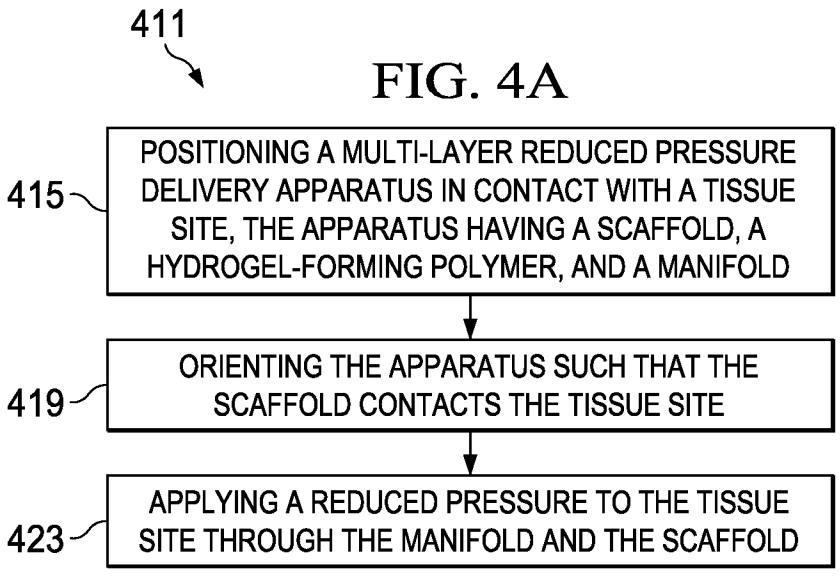

411
415
POSITIONING A MULTI-LAYER REDUCED PRESSURE DELIVERY APPARATUS IN CONTACT WITH A TISSUE SITE, THE APPARATUS HAVING A SCAFFOLD, A HYDROGEL-FORMING POLYMER, AND A MANIFOLD
419
ORIENTING THE APPARATUS SUCH THAT THE SCAFFOLD CONTACTS THE TISSUE SITE
423
APPLYING A REDUCED PRESSURE TO THE TISSUE SITE THROUGH THE MANIFOLD AND THE SCAFFOLD

FIG. 4A

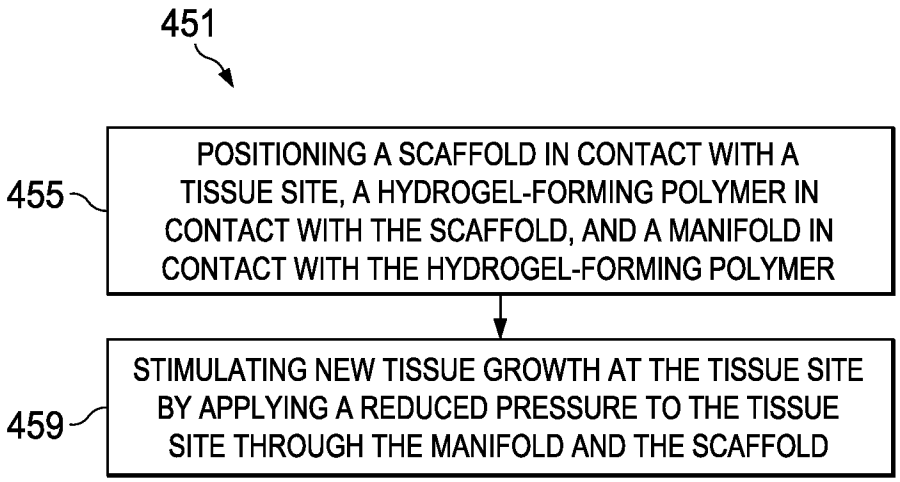
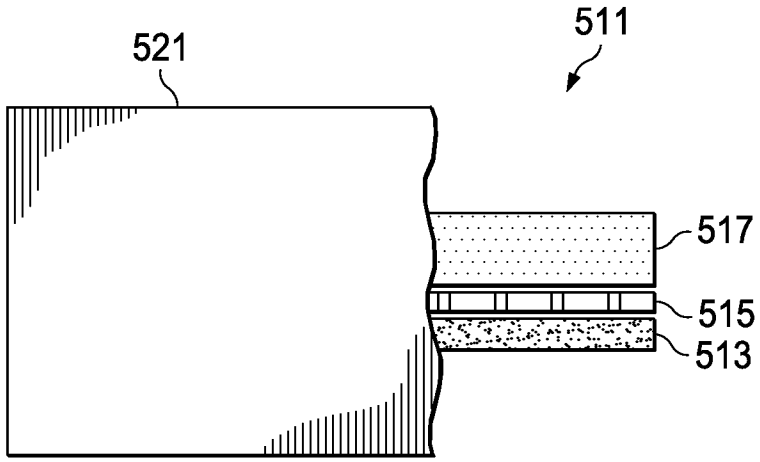

451
455
POSITIONING A SCAFFOLD IN CONTACT WITH A TISSUE SITE, A HYDROGEL-FORMING POLYMER IN CONTACT WITH THE SCAFFOLD, AND A MANIFOLD IN CONTACT WITH THE HYDROGEL-FORMING POLYMER
459
STIMULATING NEW TISSUE GROWTH AT THE TISSUE SITE BY APPLYING A REDUCED PRESSURE TO THE TISSUE SITE THROUGH THE MANIFOLD AND THE SCAFFOLD

FIG. 4B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513

FIG. 5

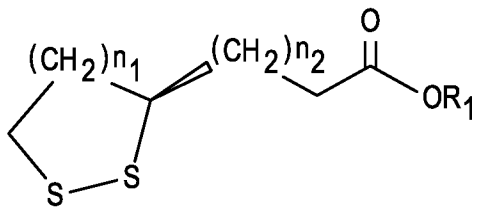


FIG. 6A

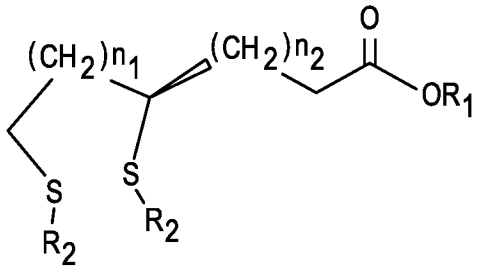


FIG. 6B

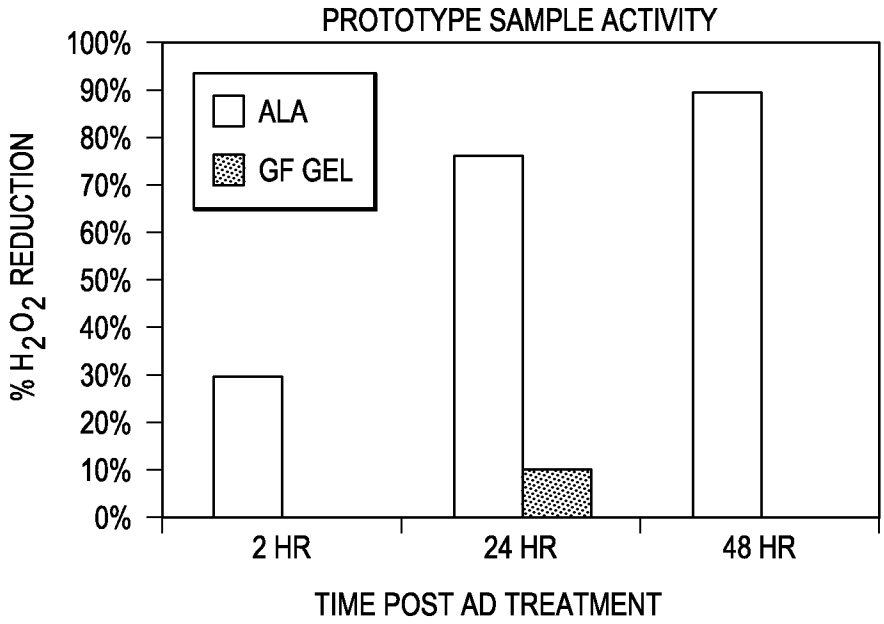


FIG. 7

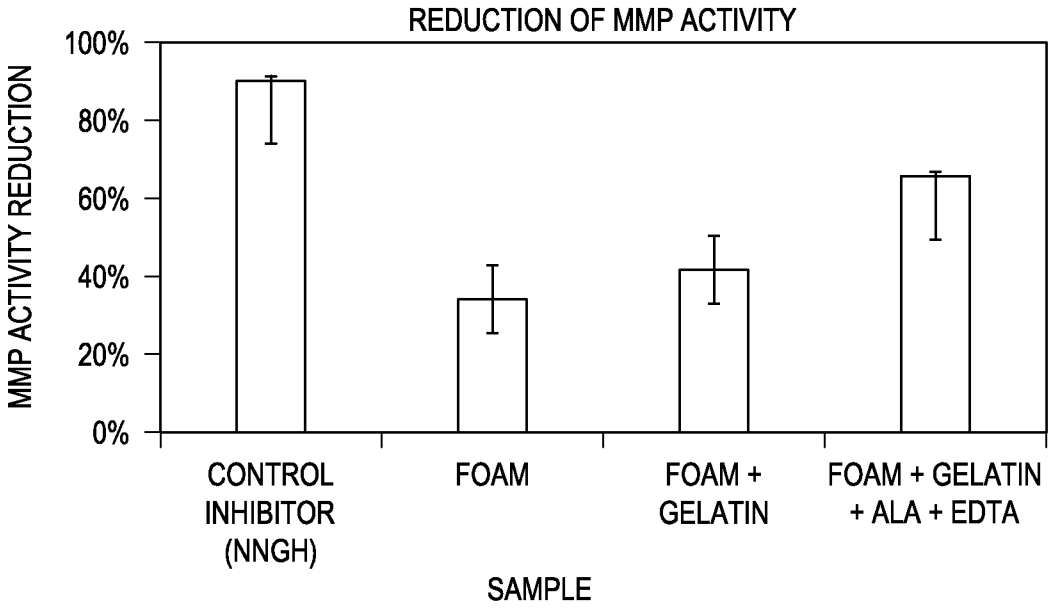
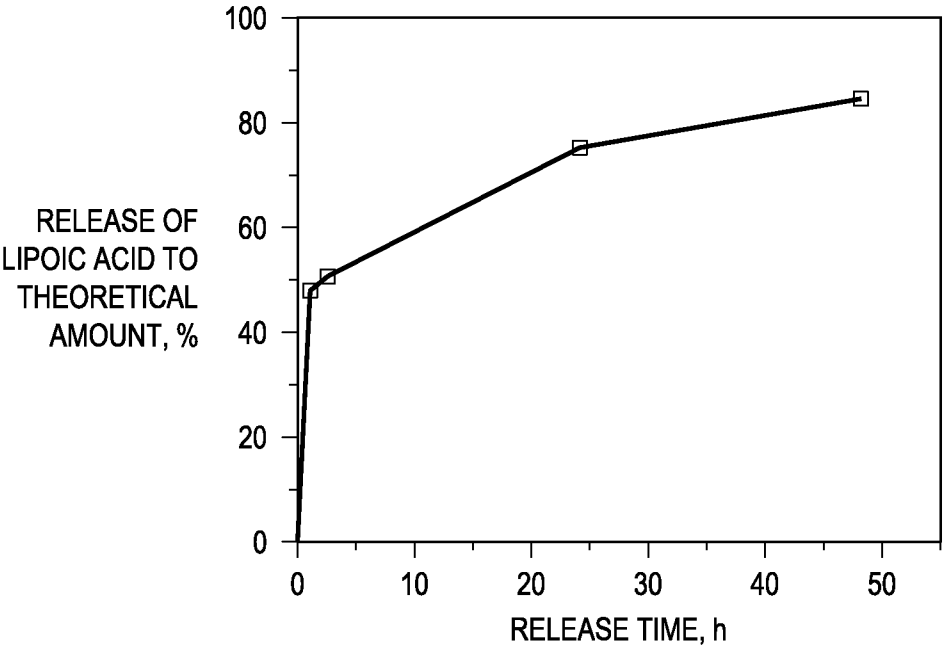

REDUCTION OF MMP ACTIVITY
MMP ACTIVITY REDUCTION
100%
80%
60%
40%
20%
0%
CONTROL INHIBITOR (NNGH)
FOAM
FOAM + GELATIN
FOAM + GELATIN + ALA + EDTA
SAMPLE

FIG. 8

FIG. 9


RELEASE OF LIPOIC ACID TO THEORETICAL AMOUNT, %
100
80
60
40
20
0
0
10
20
30
40
50
RELEASE TIME, h