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THERAPEUTIC BANDAGE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/987,494, filed March 10, 2020, the entire contents of which is incorporated by reference herein.

BACKGROUND

[0002] Chronic non-healing skin wounds and skin and soft tissue infections (SSTIs) such as those caused by methicillin resistant staphylococcus aureus (MRSA) and other bacteria are easily acquired in a variety of settings (e.g., daycare facilities, college dorm rooms, long-term care facilities, and hospitals or other healthcare establishments). SSTIs are typically treated topically, with or without high-dose antibiotic therapy. If improperly treated, these infections can penetrate deeper layers of skin, necessitating more aggressive surgical remedies to remove puss and necrotic tissue and to properly irrigate the wound. Moreover, the infection may enter blood vessels, allowing it to become established in distant tissues as well as potentially life-threatening sepsis. There are approximately 120,000 hospitalizations and 20,000 deaths per year attributable to MRSA infections, for example, but also 11.6 million ambulatory care visits per year for SSTIs, many of which are the result of chronic infections. Current treatments for these infections are costly and frequently ineffective. That is, currently available bandages do very little by way of immune modulation or the sequestration of toxins and microorganisms. Moreover, current topical treatment approaches for treating MRSA, and other SSTIs, are frequently ineffective for the following reasons: (i) poor drug delivery to dermal tissue due to the barrier function of the stratum corneum; (ii) the development of antibiotic-resistant bacterial strains including MRSA and VRSA (vancomycin-resistant Staphylococcus aureus), and (iii) a sub-optimal approach for manipulating the immunological microenvironment within the dermal tissue. Also, the current standard of care often includes minor surgery on the infection (incision and drainage) followed by high-dose oral antibiotic therapy. This approach is invasive and expensive and can result in off-target complications including disruption of the intestinal microbiome resulting in life threatening *C. difficile* infections. Further, the overuse of antibiotics is driving many microorganisms to develop antibiotic resistance, a phenomenon that the World

Health Organization characterizes as ‘one of the biggest threats to global health, food security, and development today. Finally, the known treatments are often not effective in achieving complete bacterial clearance, so infections often recur.

SUMMARY

[0003] In one embodiment, a therapeutic bandage is provided including a bandage matrix and a plurality of microneedles extending from the bandage matrix, each of the plurality of microneedles including a first layer that encapsulates a first immunomodulatory compound and a second layer that encapsulates a second immunomodulatory compound. The first layer is configured to release the first immunomodulatory agent at a first rate and the second layer is configured to release the second immunomodulatory agent at a second rate that is slower than the first rate. The first layer is positioned at a distal end of the second layer, and the second layer defining a channel extending from the distal end to the bandage matrix. The bandage matrix includes a hydration layer and a sequestration layer, the hydration layer is configured to absorb a foreign agent removed from a skin infection and the sequestration layer is configured to bind to the foreign agent removed. The bandage matrix includes a cellulose layer that is configured to bond to a biofilm resulting from the skin infection.

[0004] In another embodiments, a therapeutic bandage includes a bandage matrix and an array of microneedles extending from the bandage matrix. Each of the microneedles includes a first layer that encapsulates a first immunomodulatory compound and a second layer that encapsulates a second immunomodulatory compound. The array of microneedles is configured to guide foreign agents affected by the first immunomodulatory compound, the second immunomodulatory compound, or the first and second immunomodulatory compounds from one or more skin layers of a user to the bandage matrix such that the bandage matrix absorbs and captures the foreign agents.

[0005] In another embodiment, a therapeutic bandage includes a bandage matrix and at least one biodegradable microneedle extending from the bandage matrix. The at least one microneedle includes a base including a first end that is coupled to the bandage matrix, a second end opposite the first end, and a channel extending therethrough from the first end to the second end, and a tip coupled to the second end of the base. The tip is formed from a first material that

encapsulates a first immunomodulatory compound and the base is formed from a second material that encapsulates a second immunomodulatory compound. The first material is configured to dissolve at a first rate and the second material is configured to dissolve at a second rate that is less than the first rate. The first immunomodulatory agent and the second immunomodulatory agent establish a chemotactic gradient within one or more skin layers. The channel is configured to guide foreign agents affected by the first immunomodulatory compound, the second immunomodulatory compound, or the first and second immunomodulatory compounds from the one or more skin layers of a user to the bandage matrix such that the bandage matrix absorbs and captures the foreign agents.

[0006] In another embodiment, a method of treating a skin infection or skin condition is provided including administering, via a first layer of a microneedle, a first immunomodulatory compound beneath the skin, administering, via a second layer of the microneedle, a second immunomodulatory compound beneath the skin, and draining phagocytic cells effected by the first immunomodulatory compound and the second immunomodulatory compound through a channel in the microneedle.

[0007] In another embodiment, a method of treating a skin infection or skin condition in humans and animals includes administering, via a first layer of a microneedle, a first immunomodulatory compound to a first layer of the skin or a biofilm layer, administering, via a second layer of the microneedle, a second immunomodulatory compound to a second layer of skin or the biofilm layer, and absorbing, by a bandage matrix, foreign agent affected by the first immunomodulatory compound, the second immunomodulatory compound, or the first and second immunomodulatory compounds. The second layer of the skin may be the same or different than the first layer of the skin.

[0008] Other aspects of the invention will become apparent by consideration of the detailed description and accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1A illustrates a schematic view of a therapeutic bandage according to one embodiment.

- [0010] FIG. 1B illustrates a schematic of a portion of the therapeutic bandage of FIG. 1A.
- [0011] FIG. 1C illustrates another schematic view of the therapeutic bandage of FIG. 1A.
- [0012] FIG. 1D illustrates a schematic of a portion of the therapeutic bandage of FIG. 1A.
- [0013] FIG. 2A illustrates a portion of the therapeutic bandage of FIG. 1A and interaction with underlying tissue.
- [0014] FIG. 2B illustrates the portion of the therapeutic bandage of FIG. 1A and interaction with underlying tissue.
- [0015] FIG. 2C illustrates the portion of the therapeutic bandage of FIG. 1A and interaction with underlying tissue.
- [0016] FIG. 3A illustrates a portion of the therapeutic bandage of FIG. 1A.
- [0017] FIG. 3B illustrates another view the portion of the therapeutic bandage of FIG. 3A.
- [0018] FIG. 3C illustrates another view the portion of the therapeutic bandage of FIG. 3A.
- [0019] FIG. 4A illustrates a first portion of the therapeutic bandage of FIG. 1A.
- [0020] FIG. 4B illustrates the first portion of FIG. 4A coupled to a second portion of the therapeutic bandage of FIG. 1A.
- [0021] FIG. 4C illustrates a transverse section of explanted human skin following a therapeutic bandage application.
- [0022] FIG. 4D illustrates a longitudinal section of explanted human skin showing spacing of microneedle deposition in the dermal layer following the therapeutic bandage application.
- [0023] FIG. 4E illustrates explanted human skin showing contents released by following the therapeutic bandage application.
- [0024] FIG. 5 illustrates the epifluorescence microscopy results after contents from the therapeutic bandage are released into the skin layers of explanted skin.

[0025] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

DETAILED DESCRIPTION

[0026] Before any embodiments of the invention are explained in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the following drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways.

[0027] FIGS. 1A and 1B illustrate a therapeutic bandage 10 including a first or subcutaneous portion 14 that extends through outer layer (e.g., epidermis) of the skin 18 of a user and is positioned under the skin 18. The therapeutic bandage 10 also includes a second portion 22 that is positioned on or above the skin 18. The first portion 14 includes a plurality of dual-layer microneedles 26 (only one needle of the plurality of needles is shown in FIG. 1A), and the second portion 22 includes a bandage matrix 30. The plurality of dual-layer microneedles 26 are arranged in an array of microneedles 26 (e.g., an array with a density of about 1,200 microneedles per square inch of the bandage matrix 30). The plurality of microneedles 26 are at least temporarily coupled to the bandage matrix 30. The bandage matrix 30 is positionable or coupleable to a surface of the skin 18 such that the plurality of microneedles 26 penetrate the skin 18. That is, the microneedles 26 penetrate through the epidermis layer of the skin 18 (and the biofilm, if present) such that a portion becomes lodged in the dermis layer of the skin 18. The dermis layer is vascular.

[0028] With further reference to FIGS. 1A, 1B, 4A, and 4B, each of the plurality of microneedles 26 include a tip 40 (e.g., first needle layer) and a base 44 (e.g., second needle layer). The tip 40 is formed from a first polymeric material and encloses (e.g., suspends, encapsulates) a first immunomodulatory compound, a biological agent, an antimicrobial agent, or a combination of a immunomodulatory compound, a biological agent, and an antimicrobial agent. In the illustrated embodiment, the tip 40 is substantially conical, although the tip 40 may be other suitable shapes in other or alternative embodiments. The first polymeric material

dissolves at a first rate. The first polymeric material may be, for example, a mixture of polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA), although the first polymeric material may be any suitable material in other or alternative embodiments.

[0029] The base 44 includes a first (e.g., distal) end coupled to the tip 40, a second end coupled to the bandage matrix 30, and a channel 50 (e.g., microchannel or aperture) extending therethrough (also see FIG. 4A) between the first end and the second end. In the illustrated embodiment, the base 44 is substantially cylindrical, but in other or additional embodiments, the base 44 may be any suitable shape. The base 44 is formed from a second polymeric material. The second polymeric material may be, for example, poly(lactic-co-glycolic acid) (PLGA), although the second polymeric material may be any suitable material in other or alternative embodiments. The base 44 encloses (e.g., suspends, encapsulates) a second immunomodulatory compound. Like the tip 40, the base 44 may further enclose one or more biological agents, antimicrobial agents or both. The second polymeric material dissolves at a second rate that is slower than the first rate.

[0030] The microneedles 26 are non-toxic and biodegradable. In the illustrated embodiment, the tip 40 has a first length, and the base 44 has a second length that is equal to the first length. In the illustrated embodiment, the first length and the second length are 600 microns. In other or alternative embodiments, may have any suitable lengths. For example, in other embodiments, either or both of the first length or the second length may range from 100 microns to 600 microns. Moreover, in some embodiments, the total length of the microneedles 26 (e.g., the sum of the first length and the second length) may range from 200 microns to 1200 microns. Accordingly, and as discussed in greater detail below, the microneedles 26 are configured to deliver different biologically active compounds to different tissue depths thereby instigating a specific response for a specific type of pathogen or other foreign agent (for example, and without limitation, neoplasms, liver spots, poison ivy, poison oak, poison sumac, or tattoo ink). In some embodiments, the biologically active compounds may be instigate a specific response to other types of skin conditions, such as hereditary skin disorders (e.g., vitiligo), auto-immune disorders (e.g., lupus, scleroderma), and/or age-related degeneration of the skin (e.g., discoloration and/or wrinkling of skin). Additionally, in other or alternative embodiments, the microneedles 26 may include additional layers, which may be formed from a polymeric material and may enclose (e.g.,

suspend, encapsulate) additional immunomodulatory compounds, anti-microbial compounds, biologically active compounds, or a combination thereof. The sequential delivery of biologically active materials in close proximity to one another (via the co-localization of the tips 40 of the microneedles 26 and the base of the 44 of the microneedles 26) facilitates a two-phase movement or a three-phase movement of leukocytes into the tissue as described below by virtue of establishing chemokine gradients. This proximity augments egress of bacteria-laden leukocytes out of the tissue, via the microchannel 50 and into the bandage matrix.

[0031] In the illustrated embodiment, each of the plurality of microneedles 26 is configured to match or closely match the biological process of the infectious agent of a MRSA skin infection. In other or additional embodiments, the microneedles may be configured to match or closely match the biological processes of the infectious agents of other types of infections or other types of foreign agents. In the example of MRSA, MRSA evades host defenses in part by secreting many virulence factors, which disrupt neutrophil function. Neutrophils are recognized as the key host effector cell population for phagocytosing and killing MRSA. MRSA counteracts neutrophil function with an arsenal of its own, which includes neutrophil-killing toxins such as the Panton-Valentine leucocidin (PVL), alpha-toxin, phenol-soluble modulins, among others. In the initial stages of MRSA infection, the bacterium is only mildly pathogenic, growing in small planktonic microcolonies. Upon sensing a bacterial community, these microcolonies secrete quorum-sensing signals via a *Agr* two-component regulatory system and switch to a hyper-virulent form while initiating the formation of impenetrable biofilms. One goal of the therapeutic bandage 10 is to prevent this switch using a new class of ‘virulence inhibiting’ antibiotics, as discussed below. Neutrophils traffic into inflamed tissues following a chemotactic gradient in response to bacterial products (e.g., *N*-formylmethionyl-leucyl-phenylalanine (fMLF)), or chemokines (e.g., interleukin-8 (IL-8)) released by leukocytes and other cells, often in response to tissue damage.

[0032] Although only described in the context of a single microneedle 26, the following process applies to each of the microneedles 26 of the therapeutic bandage 10. As shown in FIG. 2A, after application of the bandage 10 to the site of interest, the polymeric material of the tip 40 begins to dissolve at the first rate, which is about 15 minutes to 30 minutes. As the tip 40 dissolves, the first immunomodulatory compound, the biological agent, and the antimicrobial

agent encapsulated in the first polymeric material are released into the tissue beneath the skin 18. As the tip 40 dissolves, neutrophils migrate out of local capillary beds and into the tissue. In the illustrated embodiment, the first immunomodulatory compound is a chemokine (or combination of chemokines), which influences the migration of white blood cells (e.g., macrophages and neutrophils) from the blood stream into the infected area. In the illustrated embodiment, the first immunomodulatory compound is IL-8 having a concentration ranging from 1 nM to 10 nM and fMLF having a concentration of ranging 200 nM to 1,000 nM, which may induce robust neutrophil infiltration and priming/activation. In other embodiments, any of the known classes of chemokines or combinations of classes of chemokines may be used. Known, classes of chemokines include, but are not limited to, lipids (e.g., PGE2, platelet activating factor (PAF)), N-formylated peptides (e.g., bacterial, mitochondrial, or other FPR1, 2 and 3 agonists, such as fMLF, fMMYALF), eicosinoids (e.g., lipoxin A4) and other small molecules (e.g. pepducins, host-derived peptides, complement anaphylotoxins (C5a), or small proteins peptides), or proteins (e.g., CXCL8 and/or CXCL2), small molecules including leukotrienes (e.g., LTB4), cytokines (e.g., interleukin-8 (IL-8), IL-17A/IL-23), methylated BSA and/or any other suitable compound.

[0033] The biological agent helps the body fight the bacteria or infection agent (e.g., MRSA) and facilitate wound disinfection by “opsinizing” bacteria to enhance phagocytosis, and/or by attracting elements of the complement system. Opsonization is the process by which microorganisms are ‘made tasty’ to phagocytes upon coating of their outer surface with antibodies or complement components. Moreover, the biological agent can also neutralize bacterial toxins. The biological agent may include an organism-specific monoclonal antibody such as anti-Gmd (or other suitable MRSA-specific antibody), anti-MecA (PBP2a), anti-alpha toxin, and/or any suitable organism-specific monoclonal antibody (e.g., monoclonal antibody). In one example, monoclonal antibodies target a MRSA surface protein known as glucosaminidase (gmd), which dramatically improves phagocytosis of planktonic MRSA as well as MRSA growing in megaclusters. This so-called ‘opsonophagocytic activity’ is initiated when the Fc portion of the monoclonal antibody is recognized by Fc-receptors (or CD14) expressed on the plasma membrane of neutrophils, triggering bacterial internalization.

[0034] The antimicrobial agents help disable the microorganism to facilitate their uptake by the naturally phagocytic cells. In the illustrated embodiment, the antimicrobial agents may

include vancomycin, daptomycin, a combination of vancomycin and daptomycin, sitafloxacin, and/or any suitable antimicrobial agent or antibiotic (e.g., apicidin, savirin, ambuic acid, or any other member of this class of antibiotics, which may further include hydroxyketones, oxacillin, peptide-conjugated locked nucleic acids, tetrapeptide derivatives, ω -hydroxyemodin, or a combination thereof). Other or additional antimicrobial agents may be used instead of or in addition to other or additional embodiments. The cells effected by the first immunomodulatory compound, the biological compound, and the antimicrobial agent (e.g., phagocytic cells) begin to disinfect the tissue beneath the skin. It should be noted that the antibiotic dose is very low in comparison to current practice (administered orally or IV), and will remain localized to the skin (predominantly) thereby avoiding many of the consequences associated with high-dose antibiotic therapy, especially on the gut microbiome. The use of very low doses of locally administered antibiotics, and the use of 'virulence inhibitors' prevents the development of antibiotic resistance since these agents provide no growth/survival advantage to bacteria (unlike traditional bactericidal/bacteriostatic antibiotics). For example, the inhibition (via a virulence inhibitor antibiotic) of the *Agr* two-component quorum-sensing regulatory system prevents biofilm production and the expression of nearly 200 downstream virulence genes, many of which inhibit neutrophil function. Moreover, the inhibition of quorum sensing signals helps maintain MRSA in a planktonic state, making the bacterium much more susceptible to phagocytosis.

[0035] With reference to FIGS. 1B, 1D, 2B, and 2C, once the tip 40 dissolves, the base 44 remains such that the channel 50 is accessible. Then the polymeric material of the base 44 begins to dissolve at the second rate, which is about 24 hours to about 72 hours. As the base 44 dissolves, the second immunomodulatory compound begins to release from the base 44, and cells effected by the contents of the tip 40 migrate towards the channel 50. More specifically, neutrophils (and/or other white blood cells, e.g., macrophages) released as the tip 40 dissolves acquire the pathogenic bacterial (e.g., infectious agent, foreign agent) within the wound and begin their migration towards the channel 50 due to the release of the second immunomodulatory compound. Because the channel 50 has the highest concentration of immunomodulatory compounds within and around an opening 54 (FIG. 1B) thereof, the phagocytic cells move toward and through the opening 54 (FIG. 2C). Accordingly, the phagocytic cells (with their recently-acquired bacterial, infectious agent or foreign agent payload) travel through the channel 50 due to capillary fluid movement, exit through the skin 18, and enter the bandage matrix 30

that is resting or adhered to the surface of the skin 18. In the illustrated embodiment, the second immunomodulatory compound is substantially similar to that of the first immunomodulatory compound. Accordingly, the second immunomodulatory compound is a combination of chemokines. Specifically, in the illustrated embodiment, the second immunomodulatory compound is IL-8 having a concentration ranging from 1 nM to 10 nM and fMLF having a concentration ranging from 200 nM to 1,000 nM. The second immunomodulatory compounds may be different than the first immunomodulatory compounds in other embodiments. Also, other or additional immunomodulatory compounds may be used instead of or in addition to the chemokines. Moreover, the biological agents, the antimicrobial agents or both discussed above may be used. If used, the biological agents, the antimicrobial agents, or both used in the base 44 may be the same or different than the biological agents, the antimicrobial agents, or both used in the tip 40.

[0036] With reference to FIGS. 1A, 1B, 2, and 3, the phagocytic cells (which often includes necrotic tissue, infectious agents, foreign agents, bacterial toxins, cellular debris and autolysis fluids) that move through the channel 50 of the base 40 of the microneedle 26 are absorbed and captured by the bandage matrix 30, which will be discussed in greater detail below.

[0037] The bandage matrix 30 includes a transparent film layer 60 (e.g., a barrier film layer formed from a polyurethane membrane), a first bandage layer 62 (e.g., hydration layer), a second bandage layer 64 (e.g., sequestration layer), and a wound contact (e.g., cellulose) layer 70. The layers may be coupled by adhesive (e.g., acrylic adhesive) or other suitable methods.

[0038] The hydration layer 62 defines a hydrodynamic gradient based on fluid capillary action using adsorbent hydrogel materials (e.g., calcium alginate) to hasten fluid efflux from the wound into the bandage matrix 30. In some embodiments, a third immunomodulatory compound may be included in the hydration layer to further attract phagocytic cells into deeper layers of the bandage matrix 30. In some embodiments, the hydration layer 62 may be formed from hydrogel impregnated with the third immunomodulatory compound (e.g., chemokine-impregnated), which is discussed in detail below. In the illustrated embodiment, the third immunomodulatory compound is substantially similar to that of the first and second immunomodulatory compounds. Accordingly, in the illustrated embodiment, the third

immunomodulatory compound is IL-8 having a concentration ranging from 1 nM to 10 nM and fMLF having a concentration ranging from 200 nM to 1,000 nM. The third immunomodulatory compound may be different than the first and second immunomodulatory compounds in other embodiments. Moreover, biological agents, antimicrobial agents, or both discussed above may be also be included in the hydration layer used. If used, the biological agents, the antimicrobial agents, or both used in the hydration layer 62 may be the same or different than the biological agents, the antimicrobial agents, or both used in the tip 40 and the base 44.

[0039] The sequestration layer 64, which is shown in FIGS. 3A-3B, may be positioned adjacent to the hydration layer 62. In the illustrated embodiment, the sequestration layer 64 includes a base layer 90 that is coupled to or coated with a capture layer 94 having one or more immobilized antibodies 98. Also, a ligand or dye 102 is bound to the one or more of the antibodies 98 as part of a detection/saturation reporter system. In the illustrated embodiment, the base layer 90 is 6% cross-linked agarose bound to protein A/G and the capture layer 94 includes monoclonal antibodies configured to attract or otherwise tightly adhere to the respective infectious agents or foreign agents (e.g., MRSA in this embodiment). The sequestration layer 64 sequesters the infectious agents or foreign agents and associated toxins. The dye 102 bound to the antibodies is released when the infectious agent or foreign agent is present. The dye 102 that is released diffuses radially into the hydration layer 62 becoming visible through the transparent film, thereby alerting the patient or healthcare worker that the therapeutic bandage 10 has reached its capacity and should be replaced.

[0040] In one specific embodiment, as wound exudate migrates into the therapeutic bandage 10, it will pass through the cellulose layer 70 (discussed below) and will encounter the base layer (e.g., the diffuse matrix of 6% beaded agarose covalently modified with Protein A or G), which binds to antibody Fc regions with high avidity. In this embodiment, the antibodies are monoclonal antibodies to Gmd, which will bind to and sequester any free bacteria which enter the bandage matrix 30. During manufacture, approximately 10% of the antibody binding sites will be occupied with recombinant Gmd-conjugated to 400 nm blue latex beads 102. As the capacity of the bandage 10 for MRSA binding is approached, the blue latex beads 102 will gradually be released, allowing them to diffuse into the hydrogel 62 where they will become visible to the naked eye through the clear, medical grade polyurethane barrier film. As noted

above, this modified lateral flow immunoassay will report bandage saturation to the health care professional, triggering bandage removal and replacement.

[0041] The cellulose layer 70 provides a mechanism for micro-debridement as the carbohydrate layer created by the cellulose intermingle with a carbohydrate layer of the infectious agent (e.g., the exopolysaccharide of the MRSA present in the biofilm at the surface of the wound) or foreign agent. That is, a biofilm developed by the wound (which often impedes proper wound healing) may grow into the cellulose layer, creating permanent points of attachment. Once the therapeutic bandage 10 is removed, the biofilm will remain associated (integral) with the cellulose layer 70, providing a mechanism for pain-free removal, obviating the need for surgical debridement. In addition, the cellulose layer 70 can serve as a reservoir for additional chemokines and anti-microbial agents should lab tests indicate such a need.

[0042] Many superficial skin wounds become chronically infected, which leads to the breakdown of the epidermis due to constant contact with bacterial enzymes and host derived toxic factors (e.g. reactive oxygen/nitrogen, proteolytic enzymes etc.). This can lead to the formation of ‘chronic, non-healing wounds’ requiring frequent surgical debridement procedures which are painful and expensive. The bacteria which colonize these wounds, including MRSA, in response to sensing quorum factor signals exit planktonic growth patterns and form biofilms which are nearly impregnable by small molecules due to the production of an exopolysaccharide protective outer shell. Accordingly, in some embodiments, the cellulose layer 70 be made of a cellulose ((C₆H₁₀O₅)_x) (25 micron pore size) into which the exopolysaccharide will attach and intertwine with the cellulose matrix. Upon removal, the biofilm will remain attached to the cellulose layer 70, providing a mechanism for micro-debridement without surgical intervention. In other embodiment, a second approach to prevent biofilm production may be in the impregnation of the hydration layer (which may include 12.5% calcium alginate hydrogel) with anti-virulence therapeutic agents such as apicidin or other suitable antimicrobial agent or antibiotic (discussed above), which, by virtue of inhibiting the agr system will also prevent the transition into biofilm production. Alginate, for example, is a naturally occurring anionic and hydrophilic polysaccharide comprised of crosslinked (1-4)-linked β-d-mannuronic acid (M) and α-l-guluronic acid (G) monomers. Impregnation of calcium alginate with apicidin and the third immunomodulatory compound may be accomplished using supercritical CO₂, among other

processes. Once the hydrogel becomes water-saturated (approximately 30-fold swelling), directional movement of water will cease, and fluid flow within the bandage 10 will become static. Thus, the remaining activity will be based on chemotaxis and drug diffusion. The impregnation of the third immunomodulatory compound may allow bacteria-laden (e.g., infectious agent-laden, foreign agent-laden, MRSA-laden) neutrophils to move several millimeters into the bandage matrix, providing a unique approach for disinfecting the wound. Taken together, these innovations may also speed healing by virtue of preventing ‘collateral damage’ from virulence factors normally released by the bacterium, and by preventing the formation of a surface biofilm.

[0043] As multiple applications of the therapeutic bandage may be needed, the penetration points of the microneedles will differ, allowing punctate healing over the entire wound bed. Thus, different portions of the wound may be at different stages in the disinfection/wound-healing process. Over time (and with repeated applications), the wound will be sufficiently disinfected to allow normal wound healing to proceed in an unhindered fashion.

[0044] FIG. 4A illustrates a microneedle base 44 showing the hollow channel 50. FIG. 4B illustrates the microneedle base 44 coupled to the rapid-dissolving tips 40, which include tattoo ink. In one embodiment, the therapeutic bandage 10 may be producing the microneedles 26 and then coupling the microneedles 26 to the bandage matrix 30. In some embodiments, the microneedles 26 may be integrally formed with a portion of the bandage matrix 30. The microneedles are produced by forming the base 44, with the microchannel 50, and loading the base 22 with the second immunomodulatory compound. The tip 40 is then produced and loaded with the first immunomodulatory compound. The tip 40 is then coupled to the base 44 to seal the microchannel 26. To test the mechanical strength of the microneedles 26, the tips 40 were loaded with insoluble tattoo ink (Figure 4B). The microneedles 26 were then applied to cultured human skin explants using a 1 Newton application force. The tips 40 were sufficiently rigid to penetrate the epidermis (Figure 4C) and deliver the tattoo ink in close proximity to dermal blood vessels (‘BV’ in Figure 4D). That is, FIG. 4C shows a transverse section of explanted human skin following bandage application, indicating the depth of penetration and payload deposition of insoluble tattoo ink into the dermal layer. More specifically, FIG. 4C shows the depth of tissue penetration and deposition of the ink after an insertion force of 1N. FIG. 4D shows the ink in the

dermal layer adjacent to blood vessels in explanted human skin. FIG. 4E illustrates a longitudinal section of explanted human skin showing spacing of microneedle deposition in the dermal layer. The kinetics of drug release were then measured using epifluorescence microscopy and two fluorescent dyes. BODIPY-vancomycin (green) was loaded in the tips 40, while sulforhodamine B was loaded into the base 44. As anticipated, the tips 40 dissolved within 30 minutes and delivered the BODIPY-vancomycin into the dermal layer of skin, with a diffusion radius of approximately 440 microns to 600 microns (FIG. 5 at A). By one hour after bandage application, the burst release of BODIPY-vancomycin (green) from the tip 40 had diffused and was no longer detectable. Conversely, the red fluorescence was released much more slowly (after about one hour) from the microneedle base 44, with approximately equal diffusion radius (FIG. 5 at D). Moreover, as shown at FIG. 5 at B, the sulforhodamine B dye was barely visible after only 30 minutes.

[0045] The therapeutic bandage 10 discussed herein is suitable for use in healthcare settings including hospitals, outpatient clinics and nursing homes, as well as for over-the-counter applications and prescription-based applications for skin infections and conditions. Also in addition to being appropriate for any bacterial, fungal or viral skin infection, the therapeutic bandage 10 discussed herein may be suitable for the foreign agents of other skin conditions, such as poison ivy/oak/sumac, minor burns, tattoo removal, bio-threat agents, acne, contact sensitivities and allergic conditions including eczema, insect stings/bites, diabetic foot ulcers, pressure ulcers, venous ulcers, etc. Additionally, as noted above, the therapeutic bandage 10 discussed herein may be suitable other types of skin conditions, such as hereditary skin disorders (e.g., vitiligo), auto-immune disorders (e.g., lupus, scleroderma), and/or age-related degeneration of the skin (e.g., discoloration and/or wrinkling of skin). Pets and other companion animals (e.g. horses and some farm animals) also suffer from dermatological skin conditions including allergic eczema, MRSA infections and others. One embodiment of the current invention could be used to treat such animals by formulating the device with species-specific therapeutic agents in keeping with accepted veterinary practices.

[0046] The therapeutic bandage 10 discussed herein provides a highly targeted local therapy and promotes more rapid healing. It relies on the precise administration of immunomodulatory compounds to orchestrate the movement of leukocytes and other cell populations known or

suspected to be associated with wound disinfection and healing, both temporally and spatially. That is, the therapeutic bandage 10 i) recruits high numbers of neutrophils (and/or other types of white blood cells, e.g., macrophages), the key type of white blood cell needed to clear the infection, into the infected tissue; (ii) manipulates the immunological environment within the dermal tissue to prevent neutrophil (and/or other types of white blood cell, e.g., macrophage) killing and maximize their ability to engulf and destroy the bacteria; and (iii) provides a mechanism for interstitial fluid movement, which facilitates the removal of pus, detritus, neutrophils (and/or other types of white blood cells, e.g., macrophages), bacterial toxins and bacteria to exit the wound and become entrapped in the bandage matrix 30. The plurality of microneedles 26 (i) deliver therapeutic agents (e.g., the first and second immunomodulatory compounds) into the dermal layer of infected skin to promote neutrophil (and/or other types of white blood cell, e.g., macrophage) movement into the wound plus additional agents to ensure their survival and maximizing their function; (ii) have a bi-directional channel allowing fluid communication between the bandage matrix 30 and the infected tissues to facilitate the egress from the wound, and (iii) a four-layer bandage matrix which entraps (e.g., absorbs and captures) wound exudate paired with a reporter system to alert healthcare workers when the bandage becomes saturated. The elements referenced above provide a 'three-phased chemokine' approach, which establishes a temporal and spatial gradient of chemo-attractants. The first wave of immunomodulatory compounds from the tip 40 of the microneedle 26 facilitates the movement of neutrophils (and/or other types of white blood cells, e.g., macrophages) first from blood into the wound, followed hours later by the second wave of immunomodulatory compounds emanating from the base 44 of the microneedle 26. The co-localization of the tips 40 of the microneedles 26 and the channel 50 is key to proper functioning helps funnel bacteria-laden (e.g., infectious agent-laden, foreign agent-laden) neutrophils (and/or other types of white blood cells, e.g., macrophages) toward the channel 50, where interstitial fluid movement will sweep them out of wound and into the bandage matrix 30. Once net fluid movement slows to a stop, the third wave of immunomodulatory compounds emanating from the water saturated hydration layer 62 will attract neutrophils (and/or other types of white blood cells, e.g., macrophages) into deeper layers of the bandage matrix 30. The immunomodulatory compounds, the biological agents, and the antimicrobial agents maximize neutrophil infiltration, prevent their inactivation, and hasten their movement out of the wound following uptake of infectious agents

(or other foreign agents) thereby facilitating rapid wound disinfection and healing and preventing the spread of infectious organisms to visceral organs and to other individuals.

[0047] Moreover, the therapeutic bandage 10 discussed herein is minimally invasive and prevents dissemination of infectious organisms to visceral tissues, thereby mitigating a potentially life-threatening condition. For example, the microneedles 26 are small enough to avoid touching nerve endings, significantly reducing pain while penetrating the stratum corneum to enable effective drug delivery into the highly vascularized dermal layer of skin. In some instances, the therapeutic bandage can be self-administered by a patient, offering a high degree of patient compliance at a significantly reduced cost.

[0048] Various features and advantages of the invention are set forth in the following claims.

CLAIMS

What is claimed is:

1. A therapeutic bandage comprising:

a bandage matrix; and

an array of microneedles extending from the bandage matrix, each of the microneedles including a first layer that encapsulates a first immunomodulatory compound and a second layer that encapsulates a second immunomodulatory compound,

wherein the array of microneedles is configured to guide foreign agents affected by the first immunomodulatory compound, the second immunomodulatory compound, or the first and second immunomodulatory compounds from one or more skin layers of a user to the bandage matrix such that the bandage matrix absorbs and captures the foreign agents.

2. The therapeutic bandage of claim 1, wherein the first layer is configured to release the first immunomodulatory agent at a first rate, and the second layer is configured to release the second immunomodulatory agent at a second rate that is less than the first rate, and wherein the first immunomodulatory agent and the second immunomodulatory agent establish a chemotactic gradient within the one or more skin layers.

3. The therapeutic bandage of claim 2, wherein the first layer defines a first length and the second layer defines a second length, the first layer being configured to release the first immunomodulatory agent at a first tissue depth, the second layer being configured to release the second immunomodulatory agent at a second tissue depth that is different than the first tissue depth.

4. The therapeutic bandage of claim 2, wherein the first layer is formed from a mixture of polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA) and the second layer is formed from poly(lactic-co-glycolic acid) (PLGA).

5. The therapeutic bandage of claim 1, wherein the second layer includes a first end that is coupled to the bandage matrix and a second end opposite the first end, the first layer being positioned at the second end of the second layer.
6. The therapeutic bandage of claim 1, wherein the second layer includes a first end that is coupled to the bandage matrix, a second end opposite the first end, and a channel extending therethrough from the first end to the second end, the channel configured to guide the foreign agents to the bandage matrix.
7. The therapeutic bandage of claim 1, wherein the bandage matrix includes a hydration layer and a sequestration layer, the hydration layer is configured to absorb the foreign agents removed from a skin infection or skin condition and the sequestration layer is configured to bind to the foreign agents.
8. The therapeutic bandage of claim 7, wherein the bandage matrix includes a cellulose layer that is configured to bond to a biofilm resulting from the skin infection or skin condition.
9. The therapeutic bandage of claim 7, wherein the sequestration layer includes an antibody and a dye that is bound to the antibody, the antibody configured to bind at least one of the foreign agents and the dye configured to release from the antibody when the antibody binds the at least one foreign agent, the dye being visible from outside the bandage matrix when released.
10. A therapeutic bandage comprising:
 - a bandage matrix; and
 - at least one biodegradable microneedle extending from the bandage matrix, the at least one microneedle including
 - a base including a first end that is coupled to the bandage matrix, a second end opposite the first end, and a channel extending therethrough from the first end to the second end, and
 - a tip coupled to the second end of the base,

wherein the tip is formed from a first material that encapsulates a first immunomodulatory compound and the base is formed from a second material that encapsulates a second immunomodulatory compound,

wherein the first material is configured to dissolve at a first rate and the second material is configured to dissolve at a second rate that is less than the first rate,

wherein the first immunomodulatory agent and the second immunomodulatory agent establish a chemotactic gradient within one or more skin layers, and

wherein the channel is configured to guide foreign agents affected by the first immunomodulatory compound, the second immunomodulatory compound, or the first and second immunomodulatory compounds from the one or more skin layers of a user to the bandage matrix such that the bandage matrix absorbs and captures foreign agents.

11. The therapeutic bandage of claim 10, wherein the first material is formed from a mixture of polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA) and the second material is formed from poly(lactic-co-glycolic acid) (PLGA).

12. The therapeutic bandage of claim 10, wherein the base defines a first length and the tip defines a second length, the tip being configured to release the first immunomodulatory compound a first tissue depth, the base being configured to release the second immunomodulatory agent at a second tissue depth that is different than the first tissue depth.

13. The therapeutic bandage of claim 10, wherein the first material encapsulates a biological agent, an antimicrobial agent, or both.

14. The therapeutic bandage of claim 10, wherein the bandage matrix includes an antibody and a dye that is bound to the antibody, the antibody configured to bind at least one of the foreign agents and the dye configured to release from the antibody when the antibody binds the at least one foreign agent, the dye being visible from outside the bandage matrix when released.

15. The therapeutic bandage of claim 14, wherein the bandage matrix includes a cellulose layer that is configured to bond a biofilm resulting from a skin infection or skin condition.

16. A method of treating a skin infection or skin condition in humans and animals, the method comprising:

administering, via a first layer of a microneedle, a first immunomodulatory compound to a first layer of the skin or a biofilm layer;

administering, via a second layer of the microneedle, a second immunomodulatory compound to a second layer of the skin or the biofilm layer, the second layer of the skin may be the same or different than the first layer of the skin; and

absorbing, by a bandage matrix, foreign agents affected by the first immunomodulatory compound, the second immunomodulatory compound, or the first and second immunomodulatory compounds.

17. The method of claim 16, wherein administering, via the first layer of a microneedle, the first immunomodulatory compound to the first layer of the skin or the biofilm layer includes releasing the first immunomodulatory compound at a first rate, and wherein administering, via the second layer of the microneedle, the second immunomodulatory compound to the second layer of the skin or the biofilm layer includes releasing the second immunomodulatory compound at a second rate that is less than the first rate.

18. The method of claim 17, wherein releasing the first immunomodulatory compound at the first rate includes releasing the first immunomodulatory compound at a first tissue depth, and wherein releasing the second immunomodulatory compound at the second rate includes releasing the second immunomodulatory compound at a second tissue depth that is different than the first depth.

19. The method of claim 16, wherein absorbing, by the bandage matrix, the foreign agents includes binding at least one of the foreign agent to an antibody contained in the bandage matrix.

20. The method of claim 19, further comprising releasing a dye in the bandage matrix when the at least one foreign agent binds to the antibody, the dye being visible from an outside of the bandage matrix.

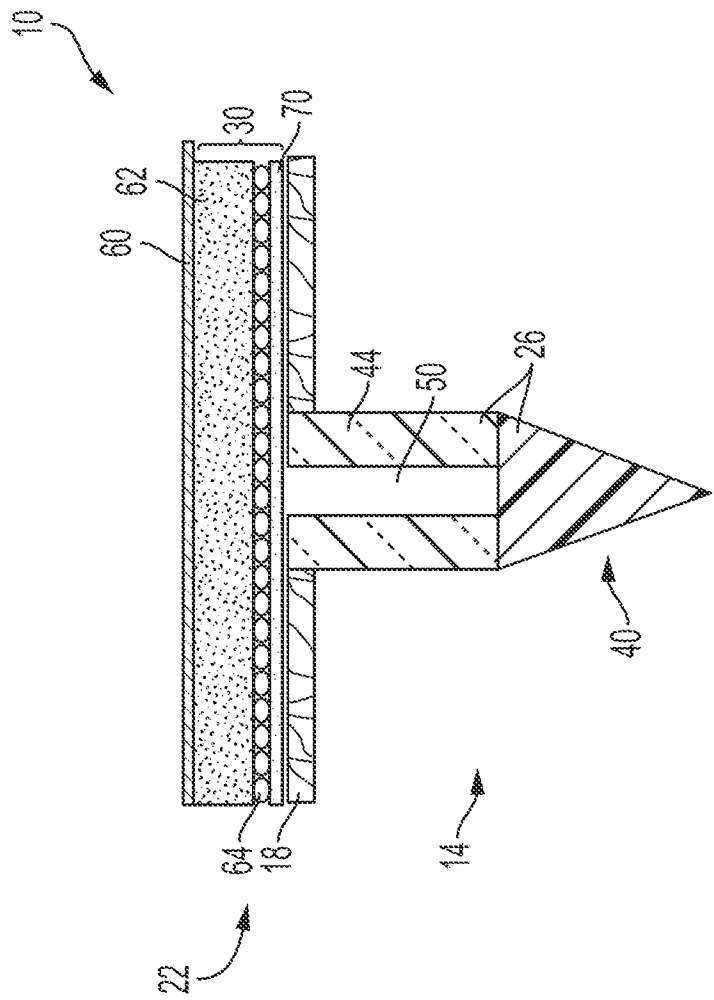


FIG. 1A

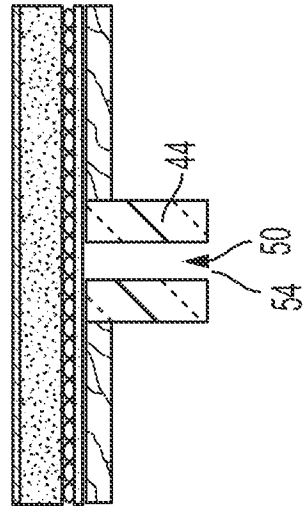


FIG. 1B

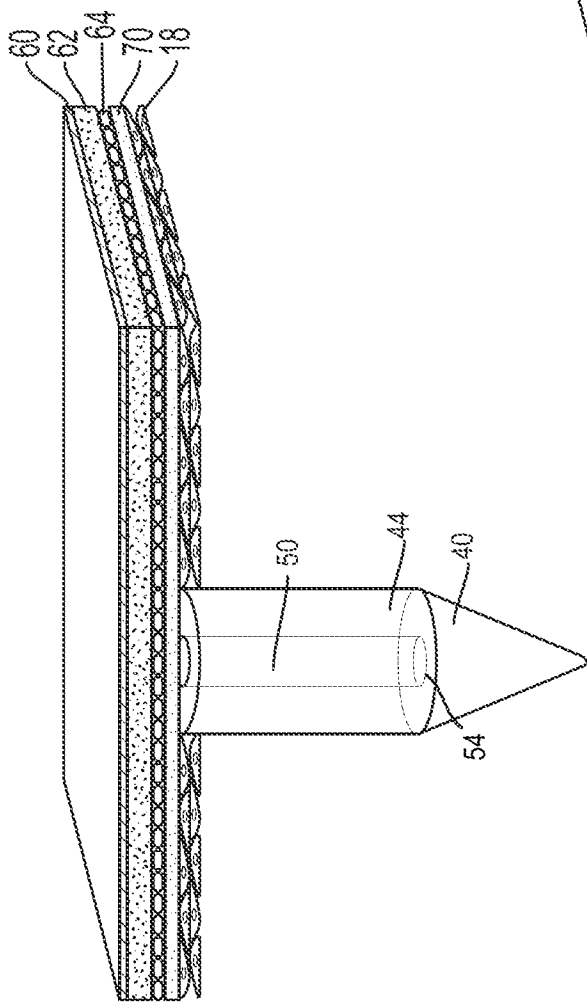


FIG. 1C

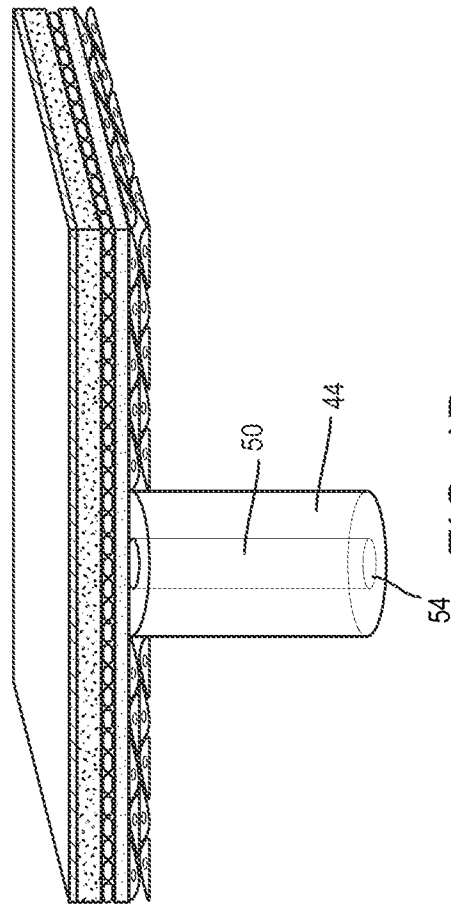


FIG. 1D

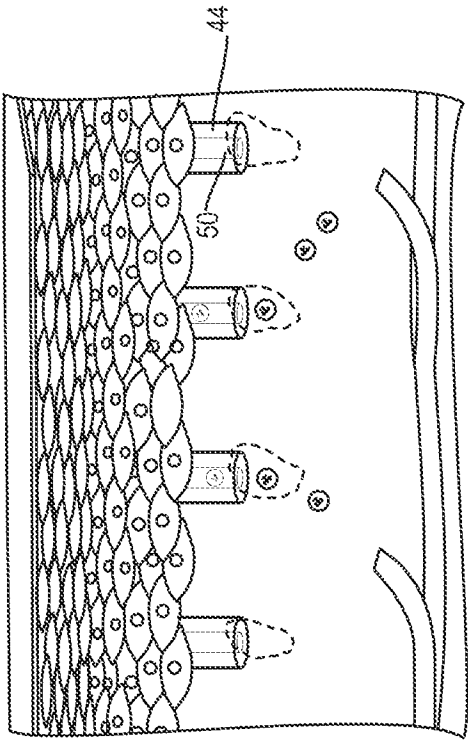


FIG. 2A

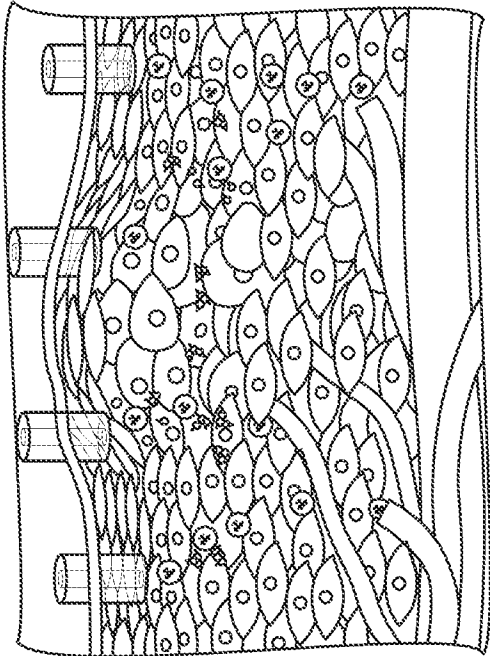


FIG. 2B

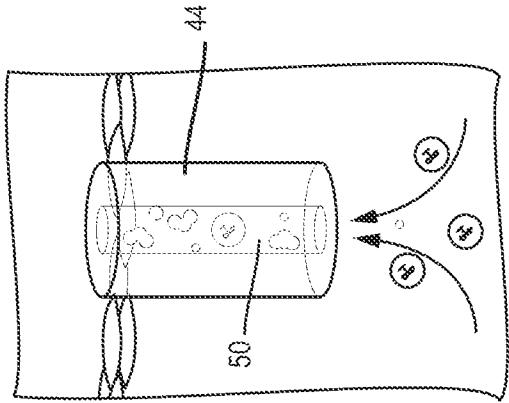


FIG. 2C

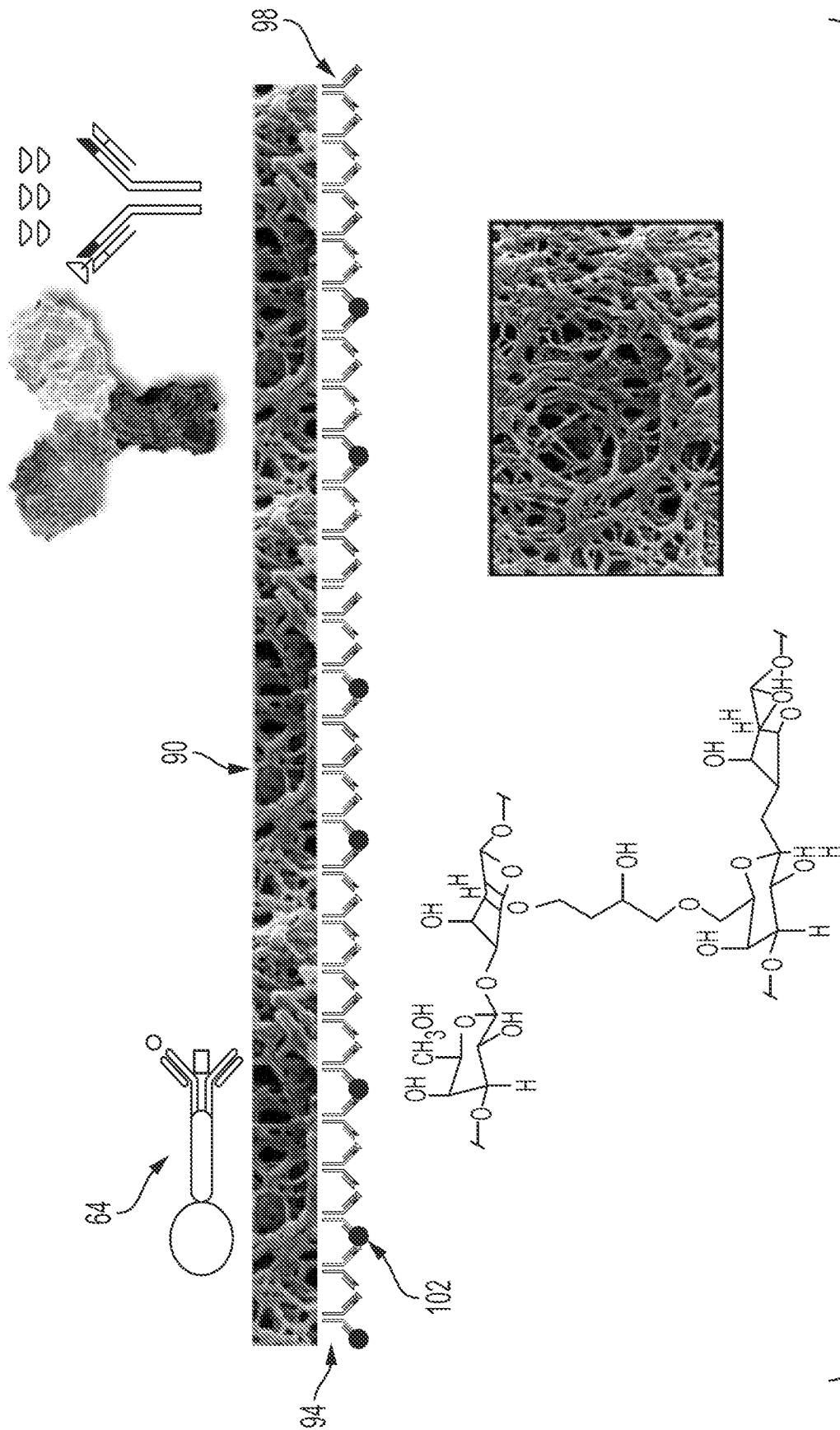
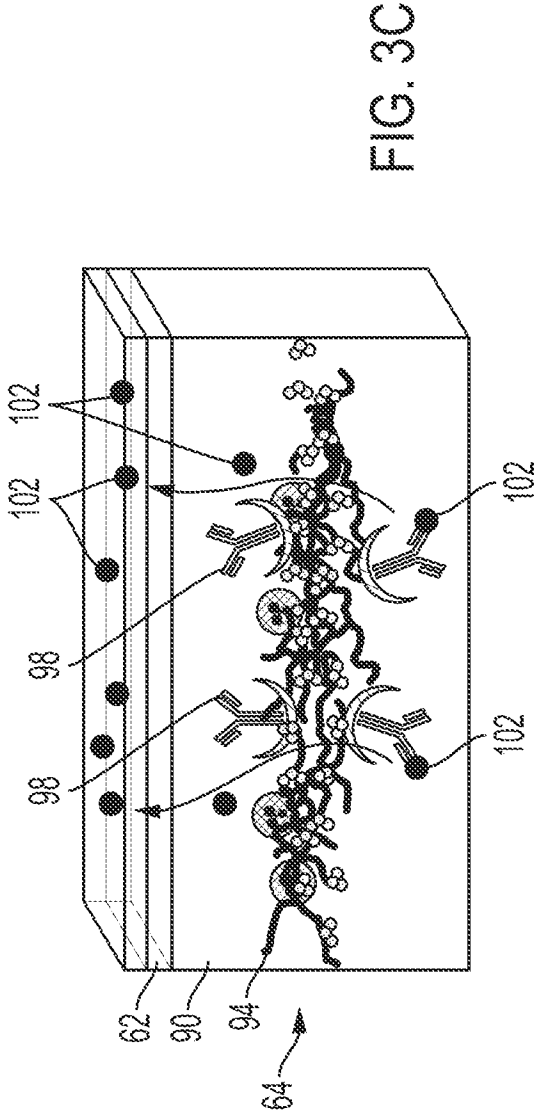
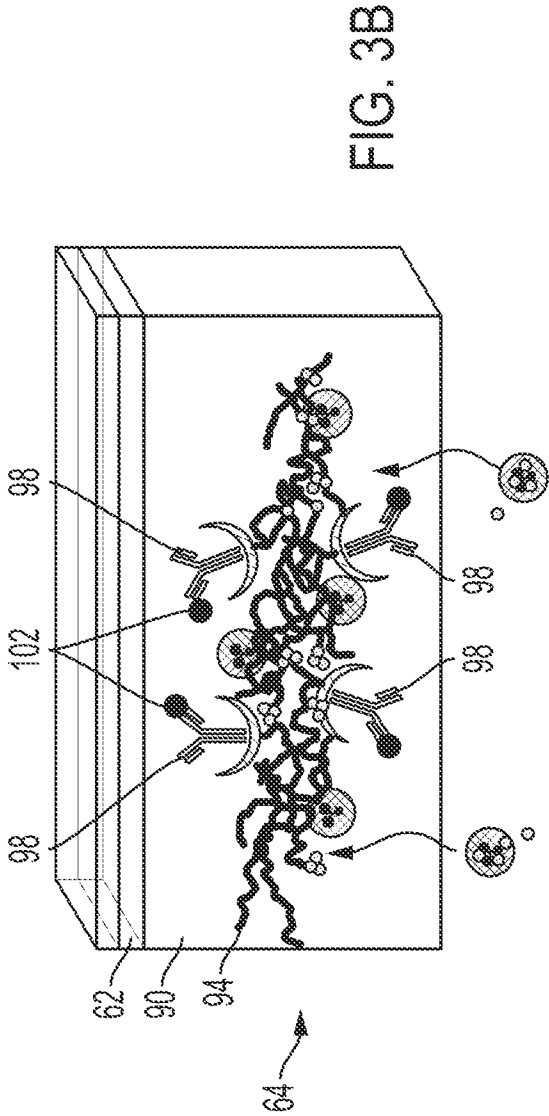


FIG. 3A



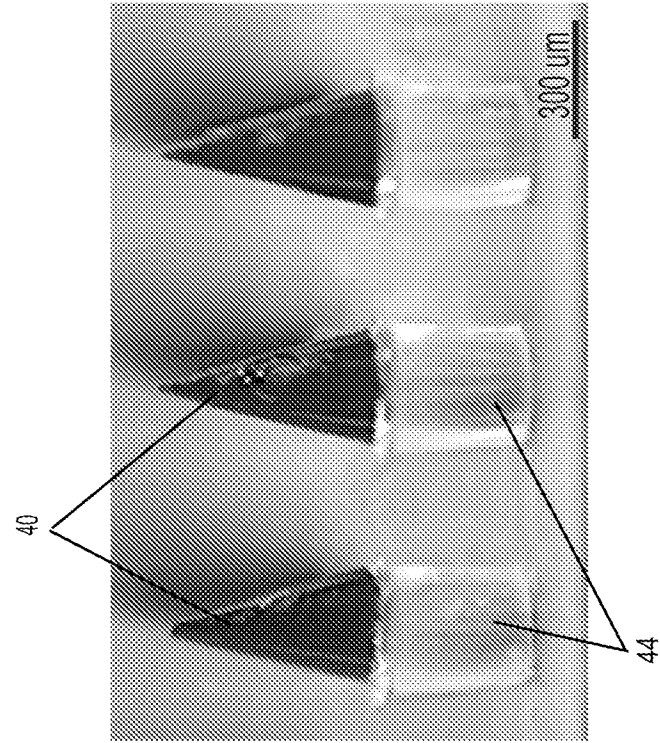


FIG. 4B

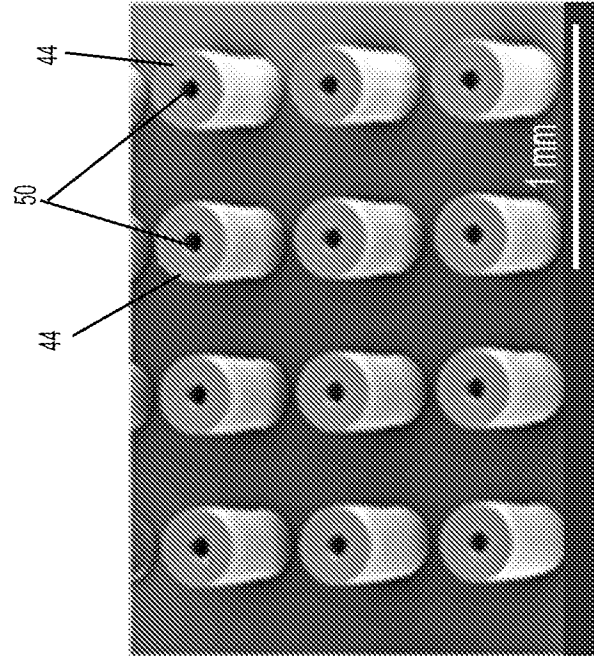


FIG. 4A

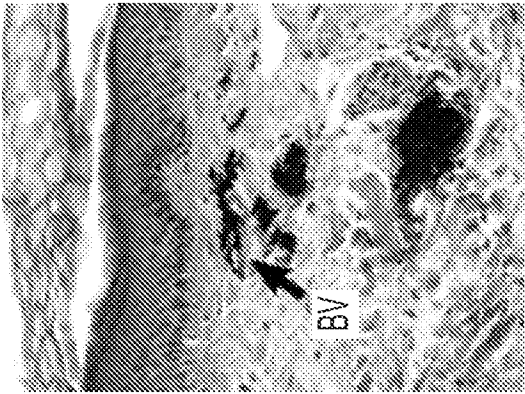


FIG. 4D

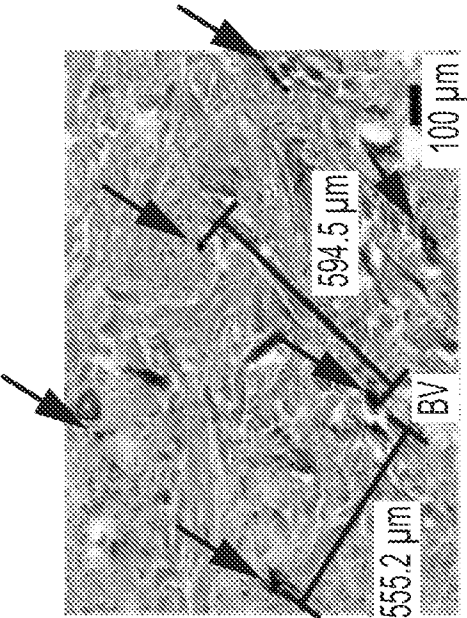


FIG. 4E

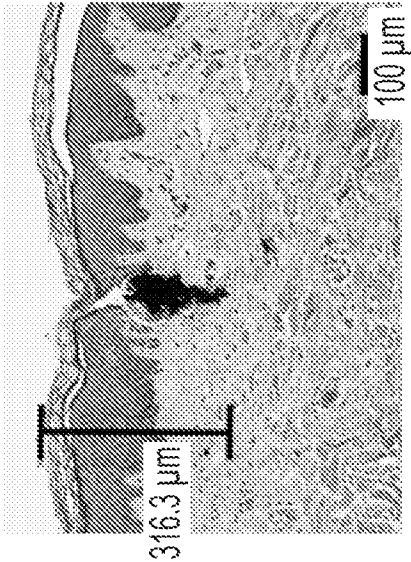


FIG. 4C

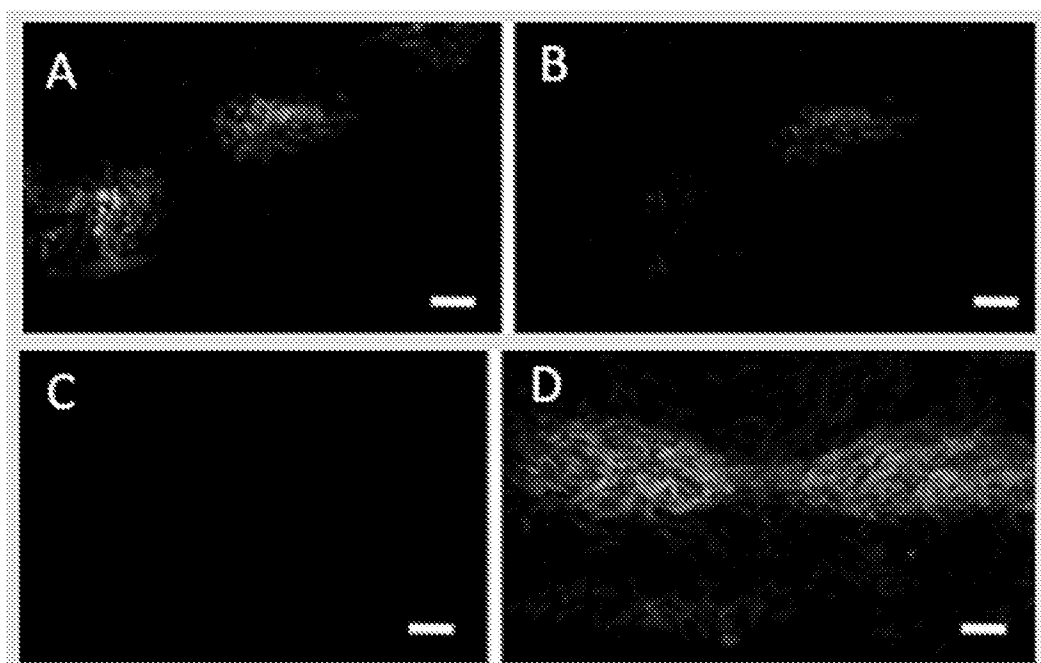


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2021/021677

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61F 13/02; A61K 9/70; A61M 37/00 (2021.01)

CPC - A61F 13/00068; A61F 13/0206; A61F 13/022; A61K 9/0021; A61M 37/0015 (2021.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

see Search History document

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

see Search History document

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

see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/0170299 A1 (GEORGIA TECH RESEARCH CORPORATION) 19 June 2014 (19.06.2014) entire document	1-20
Y	US 2018/0140817 A1 (SPECTOR) 24 May 2018 (24.05.2018) entire document	1-20
Y	US 2017/0348218 A1 (SANOVA BIOSCIENCE INC) 07 December 2017 (07.12.2017) entire document	4, 11
Y	BAGHERBAIGI et al. Cotton fabric as an immobilization matrix for low-cost and quick colorimetric enzyme-linked immunosorbent assay. Analytical Methods. 10 June 2014 (10.06.2014) entire document	7-9, 14, 15, 19, 20
Y	US 2014/0316353 A1 (RIESINGER) 23 October 2014 (23.10.2014) entire document	8, 15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

20 May 2021

Date of mailing of the international search report

JUN 22 2021

Name and mailing address of the ISA/US

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