

DECELLULARIZED PLACENTAL EXTRACELLULAR MATRIX AND USES THEREOF**PRIORITY CLAIM**

[0001] This application claims priority to United States Provisional Application No. 63/529,028 filed 26 July 2023 and is hereby incorporated by reference in its entirety.

FIELD OF INVENTION

[0002] The invention relates generally to a sterile decellularized placental derived extracellular connective tissue matrix (SDPECTM), compositions thereof, and therapeutic uses of a an SDPECTM of the present disclosure in the field of wound healing. In another aspect, an SDPECTM composition disclosed herein can be combined with umbilical cord plasma or placental - derived ingredients such as placental exosomes, placental perfusate or serum, in formulations for use in the field of wound healing, including hair follicle transplantation.

BACKGROUND

[0003] Wound healing involves a complex array of interactions among various proteins, cell types and the immune system. Basically, four steps are involved in wound healing: (1) limiting blood loss from the wound and stopping the bleeding; (2) protecting the wound area from additional damage and healing the wound; and (3) rebuilding and healing the wounded area. In step (1), platelets play a critical role in create blood clots using the protein fibrin within minutes of the creation of the wound to limit blood loss. Also during step (1), blood vessel near the wound narrow. As a result of step (a), the body stops the blood loss, the blood vessels proximate to the wound begin to relax., and the healing and cleaning processes begin. In step (2), after the bleeding has stopped, the blood vessels relax in order to bring oxygen and nutrients to the wound area. Also, white blood cells migrate to the wound area in order to begin to clean and heal the wound, as well as secrete growth factors that help the repair of the wound. In step (3), red blood cells migrate to the wound area bringing oxygen to the area. Also, cells around the wound area are directed via cell signaling to make collagen, which acts like scaffold upon which cells involved in the wound healing process can attach. The building of this scaffold results in the repair and healing of the wound. The Cleveland Clinic has reported that covering the wound helps expedite the healing process and keeps the wound cleaner.

[0004] Extracellular connective tissue matrix products are presently available for use in the management of wound healing. These products contain a scaffold made of biomaterials such as glycogen. When they are placed on the wound, the expedite the healing process

because cells involved in the process, such as, for example, fibroblasts, adhere to the scaffold, resulting in an accelerated healing process with respect to healing processes in which no prefabricated scaffold is provided. As result, the wound heals faster than it normally would, which is important limiting the possibility of infection via the wound.

[0005] These products are made of exogenous materials with respect to the subject such porcine material, bovine material, human skin (including cadaveric skin), or amniotic membrane.

[0006] What is needed is an extracellular connective tissue matrix that readily expedites the wound healing process and limits the possibility of eliciting an immune response in a patient in need of wound management, particularly from impurities that remain in the matrix after processing, such as residual material remaining in the matrix after processing.

[0007] The citation of any reference herein should not be deemed as an admission that such reference is available as prior art to the present disclosure.

SUMMARY OF THE DISCLOSURE

[0008] The present disclosure is based upon the discovery that an extracellular connective tissue matrix derived from placental matrix and is decellularized readily, has applications in the management of wounds that result from numerous injuries, including, but not limited to partial- and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled / undermined wounds, surgical wounds (donor sites/grafts, post Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, and skin tears), draining wounds and partial-thickness burns, to name only a few.

[0009] Broadly, the present disclosure extends to a sterile decellularized placental derived extracellular connective tissue matrix (SDPECTM) for use in wound management associated with a condition or disorder, comprising (a) greater than about 50% by weight placental derived collagen; (b) greater than about 10% by weight elastin; and (c) greater than about 10% moisture content, wherein the SDPECTM is substantially free of residual material.

[0010] Moreover an SDPECTM of the present disclosure can further comprise:

- (1) about less than 1% by weight:
 - (a) sulfated glycosaminoglycans;
 - (b) proteoglycans; or
 - (c) a mixture of (a) and (c);
- (2) laminin; and
- (3) fibronectin.

[0011] In a particular embodiment of an SDPECTM of the present disclosure, the residual material is not quantifiable as being not detectable, or present at an amount less than the limit of detection. Such residual material includes: (1) cells, (2) cell debris, (3) nucleic acid molecules, (4) nucleotides, (5) growth factors, (6) cytokines, (7) chemokines, (8) hormones, or (9) any combination of (1)-(8)

[0012] Moreover, the present disclosure extends to an SDPECTM as described here, wherein the following chemokines, cytokines and growth factors are not detectable in the SDPECTM or are present in the SDPECTM at an amount less than the limit of detection:

- (a) Platelet Derived Growth Factor-AA (PDGF-AA), less than the limit of detection;
- (b) platelet Derived Growth Factor-BB (PDGF-BB), not detected;
- (c) Basic Fibroblast Growth Factor beta (β FGF), not detected;
- (d) Epidermal Growth Factor (EGF), not detected;
- (e) Transforming Growth Factor beta 1 (TGF- β 1), not detected;
- (f) Hepatocyte Growth Factor (HGF), not detected;
- (g) Placental growth Factor (PLGF), not detected;
- (h) Vascular Endothelial Growth Factor (VEGF), not detected;
- (i) Insulin Like Growth Factor-1 (IGF-1), not detected;
- (j) Growth and Differentiation Factor-15 (GDF-15), less than level of detection;
- (k) Intercellular Adhesion Molecule-1 (ICAM-1), not detected;
- (l) Interleukin-10 (IL-10), not detected;
- (m) Interleukin-1 Receptor Antagonist (IL-1RA), not detected;
- (n) Interleukin-6 (IL-6), not detected;
- (o) Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF), not detected;
- (p) Interleukin-12p40 subunit (IL-12p40), not detected;
- (q) Interleukin-1 beta (IL-1 β), not detected;
- (r) Interleukin-5 (IL-5), not detected;
- (s) Interleukin-8 (IL-8), not detected;
- (t) Interleukin-13 (IL-13), not detected;
- (u) Interleukin-15 (IL-15), not detected;
- (v) Monocyte Chemoattractant Protein-1 (MCP-1), not detected;
- (w) macrophage Inflammatory Protein-1 alpha (MIP-1 α), not detected;
- (x) Regulated on Activation, Normal T Expressed and Secreted (RANTES), less than the limit of detection;
- (y) Tumor Necrosis Factor alpha (TNF α), not detected;
- (z) Human Chorionic Gonadotropin (hCG), not detected;

- (aa) Follicle Stimulating Hormone (FSH), less than the level of detection;
- (bb) Lactogen, not detected;
- (cc) Estrogen, less than the limit of detection;
- (dd) Progesterone, not detected; and
- (ee) Oxytocin, less than the limit of detection

[0013] An SDPECTM of the present disclosure can have a size that is most useful in managing a wound of subject. In a particular embodiment, an SDPECTM is in the form of particles. The sizes of the particles can vary.

[0014] The present disclosure further extends to a SDPECTM as described herein, wherein the condition or disorder with which the wound management is associated includes, but certainly is not limited to:

- (a) partial thickness wounds;
- (b) full thickness wounds;
- (c) pressure ulcers;
- (d) venous ulcers;
- (e) diabetic ulcers;
- (f) vascular disorders;
- (g) tunneled wounds;
- (h) undermined wounds;
- (i) surgical wounds;
- (j) trauma wounds;
- (k) draining wounds; or
- (l) partial-thickness burns.

[0015] The surgical wounds are wounds that result from donor and graft sites from hair transplantation, post-Mohs surgery, post-laser surgery, wounds from podiatric surgery, or wound dehiscence, to name only a few. The trauma wounds are wounds resulting from abrasions, laceration or skin tears. A variety of trauma wounds can be treated with an SDPECTM of the present disclosure. Examples include, but certainly are not limited to abrasions, lacerations and skin tears.

[0016] The present disclosure further extends to a pharmaceutical composition for wound management comprising a SDPECTM as described herein and a pharmaceutically acceptable carrier.

[0017] In addition, disclosed herein is the use of a SDPECTM of the present disclosure for use in a pharmaceutical composition for the management of wounds associated with a disease or condition in a subject in need thereof.

[0018] Numerous conditions or disorders are associated with wounds for which a SDPECTM of the present disclosure can be used to manage. Examples include, but certainly are not limited to:

- (a) partial thickness wounds;
- (b) full thickness wounds;
- (c) pressure ulcers;
- (d) venous ulcers;
- (e) diabetic ulcers;
- (f) vascular disorders;
- (g) tunneled wounds;
- (h) undermined wounds;
- (i) surgical wounds;
- (j) trauma wounds;
- (k) draining wounds; or
- (l) partial-thickness burns.

[0019] The present disclosure further extends to a method for managing wounds associated with a disease or condition in a subject, comprising administering to the subject a therapeutically effective amount of a SDPECTM or a pharmaceutical composition as disclosed herein. Such administration includes injection into a desired site in the subject, subcutaneous administration, or topical administration.

[0020] Moreover, a method of the present disclosure can further comprise the step of administering to the subject a therapeutically effective amount of a therapeutic agent such as (a) a hyaluronic acid injection at the desired site, (b) a steroid injection at the desired site, (c) an opioid injection at the desired site, (d) a biologic injection at the desired site, or (e) an antibiotic.

[0021] Such a biologic can comprise: (a) cells, (b) cell conditioned media, (c) exosomes, (d) plasma, (e) a nucleic acid molecule, (f) an antibody, (g) an anti-fungal agent, or (h) any combination of (a)-(g). The nucleic acid molecule includes DNA, RNA, mRNA, siRNA, and the antibody can be a fully human antibody, a humanized antibody, a single chain antibody (ScFv), or an active fragment of an antibody.

[0022] In such a method of the present disclosure an SDPECTM of the present disclosure a pharmaceutical composition as disclosed herein and the therapeutic agent are administered simultaneously, concomitantly, or serially.

[0023] Also provided herein is a kit comprising one or more doses of a pharmaceutical composition disclosed herein. A kit as disclosed herein may further comprise one or more

doses of a pharmaceutical composition disclosed herein. As explained above, a pharmaceutical composition of the present disclosure can comprise an SDPECTM of the disclosure and a pharmaceutically acceptable carrier, or an SDPECTM of the present disclosure and a therapeutic agent as described herein, and a pharmaceutically acceptable carrier. In a particular embodiment, a kit of the present disclosure can further comprise an appropriately sized syringe for delivery of the dose(s) of a pharmaceutical composition of the present disclosure, and an applicator for spraying the pharmaceutical composition on the wound. Moreover, 3D printing has applications in depositing a pharmaceutical composition of the present disclosing. Any 3D printing device heretofore known or subsequently discovered can be used. Alternatively, a kit of the present disclosure can comprise a first dose(s) of a pharmaceutical composition as disclosed herein comprising an SDPECTM of the present disclosure and a pharmaceutically acceptable carrier, as well as a second dose(s) of a therapeutic agent and a pharmaceutically acceptable carrier. The first and second doses can be administered simultaneous, concomitantly, or serially. It is not important which dose is given first.

[0024] These and other aspects of the present disclosure will be better appreciated by reference to the following drawings and Detailed Description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1 is a schematic of an overview of the process used to produce an SDPECTM of the present disclosure.

[0026] FIG. 2 is an SDS PAGE (8%) analysis of processed placental derived Extra Cellular Matrix (ECM) used to produce an SDPECTM compared to collagen standards. COL I is type I collagen, COL III is type III collagen, COL IV is type IV collagen, COL V is type V collagen, and COL VI is type VI collagen.

[0027] FIG. 3 is an SDS-PAGE (8%) analysis of type IV collagen detection limits. COL I is type I collagen, COL III is type III collagen, COL IV is type IV collagen.

[0028] FIG. 4 is an SDS-Page (8%) analysis of Type IV Collagen Detection limits. COL I is type I collagen, COL III is type III collagen, COL IV is type IV Collagen, COL V is type V collagen, and COL VI is type VI Collagen.

[0029] FIGS. 5A and 5B are Histology H&E Images (Low and High Magnification) of unprocessed Fresh Placental Tissue. Magnification for FIG. 5A is 40X and for FIG. 5B is 20X.

[0030] FIGS. 6A and 6B are Histology H&E Images (Low and High Magnification) of Processed ECM following the Manufacturing Process disclosed herein. Magnification for FIG. 6A is 40X and for FIG. 6B is 20X.

- [0031]** FIG. 7 is an agarose gel analysis of residual DNA in SDPECTM compositions of the present disclosure.
- [0032]** FIG. 8A is a histogram depicting cell proliferation on an SDPECTM of the present disclosure using Presto Blue assay.
- [0033]** FIG. 8B(i), (ii), and (iii) are images of cell attachment and growth on: 8B(i) Tissue Culture Plastic (TCP), 8B(ii) an SDPECTM of the present disclosure with high concentration (e.g. 5mg/well in a 48 well plate, each well 1 ml volume), and 8B(iii) an SDPECTM of the present disclosure with low concentration (e.g. 2.5mg/well in a 48 well plate, each well 1 ml volume).
- [0034]** FIG. 9A is a photograph showing attachment of cells (Tenocytes) to bovine collagen scaffolds and 9B is a photograph showing attachment of cells (Tenocytes to TCP), with both 9A and 9B having the same scale of 100µm.
- [0035]** FIG. 10 are ATR-FTIR spectra of a SDPECTM Composition.
- [0036]** FIG. 11 is a photograph of a subcutaneous injection of a disclosed SDPECTM composition.
- [0037]** FIG. 12 is an histology image of a disclosed SDPECTM composition injected subcutaneously.
- [0038]** FIG. 13 are histology images. FIG 13A is a histology image 2x magnification of a crosslinked SDCEPTM (Test article 1, TA1) composition of the present disclosure within rat 1845 two weeks after injection into the rat. FIG. 13B is a histology image 20 x magnification of a crosslinked SDCEPTM (Test article 1-TA1) composition of the present disclosure within a cell of rat 1845 two weeks after injection into the rat. FIG. 13C is a histology image 20 x magnification of a crosslinked SDCEPTM (Test article 1- TA1) composition of the present disclosure within rat 1857 twenty-six weeks after injection into the rat. FIG. 13D is a histology image of a non-crosslinked SDCEPTM (Test article 3-TA3) chorionic- derived composition of the present disclosure within rat 1857 twenty-six weeks after injection into the rat. The black arrows in FIGS. 13A-13D point to the SDCEPTM composition.
- [0039]** FIG. 14 is a histogram of particle size of a disclosed SDPECTM composition at 1-250 µm particulate size.

DETAILED DESCRIPTION

- [0040]** The present disclosure is based upon the discovery that a sterile decellularized placental derived extracellular connective tissue matrix (SDPECTM) that is substantially free of residual material and comprises greater than about 50% by weight placental derived collagen, greater than about 10% by weight elastin and greater than about 10% moisture

content can be used in the management of wounds associated with a condition or disorder, such as, *inter alia*:

- (a) partial thickness wounds;
- (b) full thickness wounds;
- (c) pressure ulcers;
- (d) venous ulcers;
- (e) diabetic ulcers;
- (f) vascular disorders;
- (g) tunneled wounds;
- (h) undermined wounds;
- (i) surgical wounds;
- (j) trauma wounds;
- (k) draining wounds; or
- (l) partial-thickness burns.

This discovery is contrary to heretofore extracellular connective tissue matrices, none of which are made from placental tissue or placental perfusate.

[0041] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure.

[0042] All numerical designations, e.g. volume, mass, number of particles, etc. are approximations which are varied by (+) or (-) by increments of 1.0 or 0.1, as appropriate. It is to be understood, although not always explicitly stated, that all numerical designations are preceded by the term "about".

[0043] Numerous terms and phrases are used throughout the present specification and claims and are defined below.

[0044] "About" and "approximately" are interchangeable and mean plus or minus a percent (e.g. $\pm 5\%$) of the number, parameter, or characteristic so qualified, which would be understood as appropriate by a skilled artisan to the scientific context in which the term is utilized.

[0045] As used here, the singular form "a", "an" and "the" include plural reference unless the context clearly dictates otherwise.

- [0046]** As used herein, the terms "comprising", "comprises" and "comprise" are intended to mean that the compositions, preparations and methods disclosed herein include recited elements, but do not exclude others.
- [0047]** As used herein, the term "concomitant" refers to a very short duration between the administration of a first therapeutic agent and a second therapeutic agent. In the present disclosure, it is not critical whether a pharmaceutical composition of the present disclosure or a therapeutic agent is administered first in concomitant administration.
- [0048]** The terms "delivery" and "administration" are used interchangeably herein and mean and include providing a "pharmaceutical composition" or "therapeutic agent" or "active agent formulation" to a treatment site, e.g., wounded tissue, through any method appropriate to deliver the functional agent or formulation or pharmaceutical composition to the wound site. Non-limiting examples of delivery methods include direct injection, percutaneous delivery and topical application at the treatment site.
- [0049]** As used herein, the terms "extracellular matrix" and "ECM" are used interchangeably herein and mean and include a collagen-rich substance that is found in between cells in mammalian tissue, and any material processed therefrom, e.g. decellularized ECM. In a particular embodiment, ECM material is derived from human placenta.
- [0050]** As used herein the phrase "wound management" refers to an ongoing treatment of a wound including the providing of an environment conducive to healing and prevention of skin breakdown. The type of wound management utilized is dependent upon the size, depth, severity and location of a wound. (Karthick, K.G., *et al.*, *Medical and Healthcare Textiles* (2010)).
- [0051]** As used herein, the terms "lyophilized" and "dehydrated" are used interchangeably, and refer to the state, but not the method of having water removed as a means of preservation.
- [0052]** The terms "patient" and "subject" are used interchangeably herein, include warm blooded mammals, humans and primates; avians; domestic household or farm animals, such as cats, dogs, sheep, goats, cattle, horses and pigs; laboratory animals, such as mice, rats and guinea pigs; fish; reptiles; zoo and wild animals; and the like.
- [0053]** As used herein, the term "placenta" refers to a disc of tissue that connects a mother's uterus to the umbilical cord and is ultimately responsible for delivering nutrients and oxygen to a fetus. Three layers of membranes make up the placenta: (1) the amnion, which is a single layer of ectodermal epithelium completely enclosing the embryo; (2) the chorion which surrounds the amniotic sac and includes the villi and trophoblast; and (3) the decidua of the

maternal endometrium. The umbilical cord is the conduit between the placenta and the mother's circulatory system, and consequently, is not a part of the placenta.

[0054] As used herein, the term "resuspended" refers to the addition of a liquid, e.g., a diluent, to a dehydrated material in order suspend the material in a solution and to allow for injection through an adequately sized needle.

[0055] As used herein, the terms "sprinkle" or "sprinkling" refer to scattering or pouring a SDPECTM or pharmaceutical composition of the present disclosure onto a wound.

[0056] As used herein, the term "stagger" or "staggered" with respect to administration of a first and second pharmaceutical composition means administration of one of the agents occurs at a different time than the administration of the administration of the second agent, such that the duration between each of the administrations is greater than the duration between the concomitant administration of two therapeutic agents.

[0057] As used herein, the term "simultaneous" or "simultaneously" with respect to the administration of a therapeutic agent as described above refers to administration of a therapeutic agent and administration of a decellularized placental derived extracellular matrix of the present disclosure, or pharmaceutical composition thereof, occurring at exactly the same time.

[0058] As used herein, the phrase "substantially free of residual material" refers to an extracellular matrix that does not contain a quantifiable amount of residual material, e.g., (1) cells, (2) cell debris, (3) nucleic acid molecules, (4) nucleotides, (5) growth factors, (6) cytokines, (7) chemokines, (8) hormones, or (9) any combination of (1)-(8).

[0059] As used herein The term "therapeutically effective", as used herein, means that the amount of a "pharmaceutical composition" and/or "biologically active agent" and/or "active agent formulation" administered is of sufficient quantity to ameliorate one or more causes, symptoms, or sequelae of a disease or condition. Such amelioration only requires a reduction or alteration, not necessarily elimination, of the cause, symptom, or sequelae of a disease or disorder. A therapeutically effective amount will depend on several factors including severity and course of the disease or condition, previous therapy, the patient's health status, age, weight, and response to the drugs. It is considered well within the skill of the art for one to determine therapeutically effective amounts by routine experimentation (including, but not limited to, a dose escalation clinical trial).

[0060] As used herein, the term "wound" refers to an injury to living tissue caused by a cut, blow, or other impact, typically one in which the skin is cut or broken. The motive for the wound is not important as wounds can occur naturally (such as, for example, via acne, skin

tags, etc.) or intentionally, such, as, for example from surgery, including but not limited to autologous hair follicle transplantation.

[0061] For the purposes of this application, the terms "treatment", "therapeutic use", and "medicinal use" shall refer to any and all uses of the an SDPECTM of the present disclosure to remedy a disease state or one or more symptoms, or otherwise prevent, hinder, retard, or reverse the progression of a wound in any way whatsoever.

[0062] As used herein, the phrase "Pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans.

[0063] As used herein, the term "excipient" refers to a diluent, adjuvant, or carrier with which a compound of the invention is administered. In general, sterile water, oil, saline, aqueous dextrose (glucose), polysorbate and related sugar solutions and glycols such as propylene glycol or polyethylene glycols, proteins (e.g., serum albumin), are suitable carriers for parenteral or transdermal solutions. Solutions or emulsions for parenteral or transdermal administration may further contain about 5-15% polysorbate 80 or lecithin, suitable stabilizing agents and, if necessary, buffer substances. Antioxidizing agents such as, but not limited to, sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also useful are citric acid and its salts, and sodium EDTA. In addition, parenteral and transdermal solutions can contain preservatives including, but not limited to, benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

[0064] As used herein, the phrase "therapeutically effective amount" means the amount of a SDPECTM of the present disclosure that, when administered to a subject to management the healing of wound associated with a disease, disorder or condition,

[0065] is sufficient to effect such treatment for the wound. The "therapeutically effective amount" can vary depending on the depth, size, severity of the wound, and the age, weight, etc., of the subject having the wound to be treated.

[0066] As used herein, the terms "treating" or "treatment" of any of a wound associated with a disease, condition or disorder involves ameliorating or reducing the size and depth of the wound. In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, e.g., a wound, which may not be discernible by the subject. In yet another embodiment, "treating" or "treatment" refers to administration of an SDPECTM the present disclosure to a wound for cosmetic or aesthetic purposes.

[0067] In general, sterile water, oil, saline, aqueous dextrose (glucose), polysorbate and related sugar solutions and glycols such as propylene glycol or polyethylene glycols, are

suitable carriers for parenteral solutions. Solutions or emulsions for parenteral administration preferably contain about 5-15% polysorbate 80 or lecithin, suitable stabilizing agents and, if necessary, buffer substances. Antioxidizing agents such as, but not limited to, sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also useful are citric acid and its salts, and sodium EDTA. In addition, parenteral solutions can contain preservatives including, but not limited to, benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

[0068] As explained above, the provided herein is a sterile decellularized placental derived extracellular connective tissue matrix (SDPECTM) for use in management of a wound associated with a disease, disorder, or condition comprising collagen and elastin, as well as associated methods of making and using the same for clinical applications in wound healing and aesthetics, including but not limited to the management of wounds including: partial- and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled / undermined wounds, surgical wounds (donor sites/grafts, post Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, and skin tears), draining wounds and partial-thickness burns.

[0069] An SDPECTM, as well as pharmaceutical compositions thereof are composed of 100% decellularized placental extracellular matrix (ECM), predominantly collagen, which is processed into a particulate form and terminally sterilized. A SDPECTM of the present disclosure can be crosslinked or used without crosslinking. In crosslinked forms of an SDPECTM, the crosslinking method used can be chemical (using glutaraldehyde, formaldehyde, genipin, EDC, NHS), enzymatic (transglutaminase), UV, physical, or heat (at high temperatures).

[0070] To confirm the decellularization processing effectiveness for an SDPECTM of the present disclosure, the presence of several relevant cytokines/chemokines, growth factors and major regulators of wound healing, scarring and fibrosis, as well as anti- and pro-inflammatory factors both prior to and post processing of an SDPECTM of the present disclosure, were tested. The results showed below the limit of detection (LOD) or not detected (ND) levels of these factors in the an SDPECTM of the present disclosure. Moreover, the presence of several maternal hormones were also tested for unprocessed and processed an SDPECTM of the present disclosure and resulted in below the limit of detection (LOD) or not detected (ND) post processing.

[0071] The process to manufacture an SDPECTM of the present disclosure was designed to enrich the collagen content by inclusion of an acid/base treatment, resulting in a predominantly collagen based SDPECTM of the present disclosure.

[0072] An SDPECTM as disclosed herein is enriched for the content of a developmentally early collagen, in its most non-altered, pure structural form, provide novel benefits and uses. When a wound occurs, the body utilizes collagen to form a scaffold, providing a framework for new cells to migrate and regenerate the damaged tissue. An SDPECTM of the present disclosure facilitate cell adhesion, allowing various cells involved in the wound healing process, such as fibroblasts, keratinocytes, and endothelial cells, to adhere and migrate to the wound site, and supports the formation of new blood vessels (angiogenesis) necessary to supply oxygen and nutrients to the healing tissue, which aid wound repair and aesthetic processes. The proper deposition and organization of collagen fibers during wound healing determines the quality of scar formation. Adequate collagen production helps to form stronger, more resilient, and durable tissue. An SDPECTM of the present disclosure will be essential for maintaining the skin's structure, firmness, and elasticity - providing support and volume, keeping the skin plump and smooth. As with age, natural collagen production decreases, leading to the formation of wrinkles and fine lines, an SDPECTM of the present disclosure as well as pharmaceutical compositions thereof can fill dermal defects to restore lost volume, reducing the appearance of wrinkles and enhancing facial contours, or to enhance volume and add definition to the cheeks, providing a more youthful and attractive appearance; also can improve the appearance of scars, including those resulting from acne, by filling in depressions and smoothing the skin's surface.

[0073] The ability of an SDPECTM of the present disclosure to promote tissue regeneration, support cell migration, and maintain skin structure makes it important in both medical and aesthetic applications. Various medical treatments and cosmetic procedures will improve based on the properties of an SDPECTM of the present disclosure to aid in wound repair and provide aesthetic enhancements, improving the overall well-being and confidence of individuals.

[0074] An SDPECTM as well as pharmaceutical compositions thereof for use in the management of wounds including partial- and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled / undermined wounds, surgical wounds (donor sites/grafts, post Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, and skin tears), draining wounds, and partial-thickness burns. A disclosed SDPECTM is not meant to achieve its primary intended purpose through chemical action (pharmacological activity) nor dependent upon being metabolized.

[0075] The process for manufacturing an SDPECTM of the present disclosure includes steps to decellularize a whole placenta by removal of all cells, any cellular debris, residual nucleic

acids, cytokines/chemokines, hormones, growth factors, and other regulators of wound healing, scarring and fibrosis, as well as anti- and pro-inflammatory factors and processing reagents such as salt, and detergent, resulting in decellularized placental ECM which is then subjected to lyophilization followed by a cryomilling step. An SDPECTM as disclosed herein as well as pharmaceutical compositions thereof are provided in a dry powder form, in vials with screw cap closures that are packaged in a double foil pouch sealed and provided within a carton. The packaged vials containing an SDPECTM are terminally sterilized.

[0076] In a clinical setting, an SDPECTM of the present disclosure, as well compositions thereof, are hydrated in sterile saline solution at ratio of weight by volume. For example, 100 mg of a disclosed SDPECTM is hydrated with 0.6 ml sterile saline for approximately 30 seconds and resulting paste is aspirated into a syringe and applied onto a wound. An SDPECTM as disclosed herein as well as pharmaceutical compositions thereof function as a temporary wound cover which is slowly resorbed during the wound healing process. In one aspect of this invention, an SDPECTM of the present disclosure as well as pharmaceutical compositions thereof are substantially devoid of any cellular or biological activity (i.e., absence of residual materials such as cells, chemokine/cytokines, growth factors or hormones, etc.).

Manufacturing an SDPECTM of the Present Disclosure

[0077] In the manufacturing process, decellularized human placental derived ECM is sourced from placentas of normal, healthy, full-term pregnancies. The placental starting material is sourced by established methods designed to reduce the risk of additional contamination and prevent mislabeling and/or tracking errors. These methods are consistent with regulatory requirements outlined in 21 Code of Federal Regulations (CFR) 1271, Subpart C (Donor Eligibility) and Subpart D (Good Tissue Practices). The tissues are collected from accredited hospitals by licensed health care professionals. A tissue collection kit is utilized and includes sufficient containers and barcoded labels for biomaterials along with appropriate documentation and instructions for collecting the placentas.

[0078] The placental decellularization steps are designed to remove substantially all residual material, e.g., cells, cell debris, residual nucleic acids, cytokines/chemokines, growth factors, hormones, and major regulators of wound healing, scarring and fibrosis, as well as anti- and pro-inflammatory factors, and any residual process reagents. These steps involve osmotic shocks, detergent, and acid/base treatment as well as cryomilling and terminal sterilization of the final product. The processing of placental derived ECM is conducted following ASTM-

F3354 Standard Guide for Evaluating Extracellular Matrix Decellularization Processes using aseptic technique in a biological safety cabinet.

[0079] The production of decellularized placental derived ECM is the first step in generating a composition of an SDPECTM of the present disclosure. The ECM component is sourced from whole placentas, from which the umbilical cord is removed. The placenta is cleaned to remove excess blood and blood clots and cut into small 0.5 x 0.5-inch segments. The cut placental segments are suspended in sterile water and are homogenized using an Omni mixer homogenizer. The homogenization step serves to generate small tissue particulates, with increased surface area, allowing for more effective separation and removal of cells and cellular debris from the placental tissue. The homogenized tissue from a placenta is transferred into a sterile processing container and washed repeatedly with sterile NaCl by shaking on an orbital shaker; the NaCl solution is exchanged by centrifugation to settle tissue particulate, followed by removal of the supernatant, and refreshed with additional sterile NaCl solution. The placental tissue is incubated at controlled room temperature while shaking in sterile NaCl solution, followed by centrifugation to remove supernatant, and washed with sterile water. The exposure of the placental tissue to NaCl, followed by water constitutes an "osmotic shock" to the tissue. The osmotic shock serves to remove blood, blood components, cells, and cell debris from the tissue. The placental tissue is subjected to a second osmotic shock before a nucleic acid removal step.

[0080] Following removal of nucleic acids, several extensive sterile water rinses take place, and the tissue is subjected to detergent washes to remove residuals such as cells, cell membranes, and other cell debris.

[0081] Upon completion of the detergent washes, the tissue is washed with sterile water to remove debris and residual detergent. To enrich the collagen content, the placental derived ECM is treated with sodium hydroxide solution to denature and remove any soluble non-crosslinked proteins, i.e., cytokines/chemokines, growth factors, and hormones. Thereafter, the ECM is subjected to hydrochloric acid treatment to neutralize the NaOH. Thereafter, extensive sterile water washes are conducted prior to centrifugation of the suspension to neutralize the ECM, minimize hydrolysis of the collagen, and to further facilitate the removal of solubilized product residuals such as cells, cellular debris, nucleic acids, growth factors, chemokines/cytokines, hormones, and process reagents, such as salt. The decellularized placental derived ECM is transferred into a sterile disposable tray, frozen, lyophilized and stored at room temperature in an enclosed container. The lyophilized placental derived ECM is utilized in an SDPECTM composition processing steps. A schematic view of this process is set forth in FIG.1

[0082] In summary, the processing of the decellularized placental derived ECM is designed to enrich the collagen content and substantially remove all residual material, such as cells, cell debris, nucleic acids, cytokines/chemokines, growth factors and major regulators of wound healing, scarring and fibrosis, as well as anti- and pro-inflammatory factors, and hormones.

[0083] The present disclosure may be better understood by reference to the following non-limiting examples, which are provided as exemplary of the disclosure. The following examples are presented in order to more fully illustrate the preferred embodiments of the disclosure. They should in no way be construed, however, as limiting the broad scope of the disclosure.

Example 1: SDPECTM Composition Processing Steps

[0084] To generate SDPECTM finished compositions, decellularized placental derived ECM is lyophilized and subjected to a cryomilling step to generate particulate. The lyophilized ECM is aseptically cut into smaller 2x1cm pieces. The small pieces are then subjected to cryomilling parameters such as initial cool time, grind time and frequency, and interval cooling time. Through changing these parameters, a program was created and repeated for different lots to achieve particulates under a specific particle size range $\leq 1000 \mu\text{m}$. A smaller particulate size was generated using a different program in the range of $\leq 300 \mu\text{m}$ or $\leq 200 \mu\text{m}$. In variations of the process, milled ECM is crosslinked using various methods or used in a non-crosslinked format for certain applications and taken for next steps of packaging and sterilization.

[0085] An SDPECTM as well as pharmaceutical compositions thereof are packaged in vials or other sterility maintaining containers and a secondary container, and a foil pouch, inside a carton, terminally sterilized by irradiation.

Characterization of an SDPECTM of the Present Disclosure

[0086] An SDPECTM of the present disclosure as well as pharmaceutical compositions thereof are based on decellularized human placental derived extracellular matrix (ECM), which is enriched for collagen and other minor components, as listed in Table 1.

Table 1

Characteristics of an SDPECTM of the Present disclosure

Parameter	Description
Composition	Decellularized Placental derived Extracellular Matrix (ECM) enriched for collagen
Physical Characteristics	Physical State: Dry (lyophilized) Product Form: Particulate

Parameter	Description
	Particle Size $\leq 1000 \mu\text{m}$, or $\leq 300 \mu\text{m}$ or $\leq 200 \mu\text{m}$ Product Configuration: 50 mg, 150 mg, 200 mg, 500mg Color: White to off-white
Sterilization	Sterility test shows no growth after Sterilization by irradiation. Bioburden: SAL $< 10^{-6}$
Storage and Shipping	Ambient room temperature (15°C to 30°C)
Packaging	Sealed sterile syringe or vial, pre-printed carton
Application	Rehydrate at room (ambient) temperature using sterile saline solution. An SDPECTM of the present disclosure can conform to the geometry of the wound.

Mm: micrometer; SAL: Sterility Assurance Level; C: Celsius

Example 2: Decellularized Placental Derived ECM Characterization

[0087] The decellularized placental derived ECM is composed of collagen (>50%), elastin (>10%) and very low levels of sulfated Glycosaminoglycans (sGAGs) Laminin and Fibronectin. Moisture content represents greater than 10% making up the remaining weight as depicted in Table 2.

Table 2
Decellularized Placental Derived ECM Biochemical Composition

Component	Rounded Average (Range)	Test Method
Collagen	> 50%	Hydroxyproline-based Colorimetric Method
Elastin	> 10%	TPPS Dye-based Colorimetric Method
Moisture Content	> 10%	Karl Fischer USP Method
Sulfated Glycosaminoglycans (sGAGs)/ Proteoglycans	< 1%	Blyscan Dye-Binding Colorimetric Method
Laminin	Low to undetectable	ELISA
Fibronectin	Low to undetectable	ELISA

N/A: Not Applicable; ND: Not Detected; TPPS: 5,10,15,20-tetraphenyl-21H,23H-porphine tetra-sulfonate; ELISA: Enzyme-linked Immunosorbent Assay

Example 3: SDS PAGE Analysis for Collagen Types

[0088] To investigate the collagen types in an SDPECTM of the present disclosure an analysis using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was conducted for collagen Types I, III, IV, V and VI by molecular weight and comparison to respective human placental collagen standards as per ASTM 2122-19 1 (See FIG. 2, FIG. 3 and FIG. 4). In FIGS 2-4 the following abbreviations are used:

SDS-PAGE: sodium dodecyl sulphate polyacrylamide gel electrophoresis;

MW: molecular weight (kDa);

COL I: type I collagen;

COL III: type III collagen;

COL IV: type IV collagen;

COL V: type V collagen;

COL VI: type VI collagen.

For collagen standards, higher load was used to ensure that all protein bands are visible. The faint bands of low molecular weight less than 70 kDa in collagen standards belong to impurities contained in the samples, as per their respective manufacturer's Certificate of Analysis.

[0089] Molecular Weight Marker (M) and five Collagen Standards, Collagen Type I, Type III, Type IV, Type V and Type VI (Figure 2 Lane # 1 – 5) and five lots of ECM (Lane # 6-10), were loaded into the gel. The banding pattern of ECM samples was compared with the banding patterns of the Collagen Standards to identify the presence of each Collagen Type.

[0090] Determination of the SDS-PAGE gel LOD was performed along with the sample analysis by loading Collagen Type IV standard in progressively smaller amount (3 - 0.2 µg) to establish the lowest detectable level of Collagen Type IV by evaluating the presence of characteristic banding pattern, refer to Lanes 3, 4, 5, and 6 of FIG. 2.

[0091] The results confirm that the predominant bands in processed ECM correspond to Collagen Type I and Type III as the alpha 1 Type I Collagen and alpha 1 Type III Collagen chains move at the same rate on SDS-PAGE gel with overlapping gel band patterns (Figure 2). Collagen Type IV was below the assay limit of detection (LOD) (Figure 3 and Figure 4). Collagen Type V and VI were not detectable in ECM due to lack of their signature bands (Figure 2, and Figure 4). Only the protein bands corresponding to Collagen Type I and Type III were identified.

[0092] For confirmation of gel detection limit, collagen Type IV standard was titrated further to 0.1 µg load. Refer to lanes 3, 4, 5, and 6 of FIG. 3. Collagen Type V (Lane 7)

and collagen Type VI (Lane 8) as well as two ECM samples were included (Lanes 9 and 10).

[0093] At 0.1 µg protein load, all the protein bands characteristic for Collagen Type IV are not detectable (Figure 4), therefore 0.2 µg is the lowest limit of detection (LOD) level determined for the SDS-PAGE analysis (Figure 3).

[0094] Collagen Type IV was below the assay limit of detection (LOD). Collagen Type V and VI were not detectable in ECM due to lack of their signature bands. Only the protein bands representing Collagen type I and Collagen type III were observed. These Collagen types represent the majority of the Collagen content in the placental derived ECM.

Example 4: Product use and Residuals

[0095] The processing of placental derived ECM also includes steps to ensure removal of all cells, any cellular debris, residual nucleic acids, and processing reagents such as salt, and detergent. The processed decellularized placental derived ECM that is free of residuals is used for making the final SDPECTM compositions, by subjecting the lyophilized decellularized placental derived ECM to a cryomilling step, following by packaging and terminal sterilization by irradiation.

[0096] Moreover, the placental derived ECM decellularization process is designed to remove cytokines/ chemokines, growth factors and major regulators of wound healing, scarring and fibrosis, as well as anti- and pro-inflammatory factors, and hormones. The results showed below the limit of detection (LOD) or not detected (ND) levels of these factors in the final ECM confirming the effectiveness and robustness of the ECM decellularization process.

Table 3

Calculated Values of Cytokines/Chemokines and Growth Factors in pg/mg Tissue in unprocessed placenta as Compared to Processed ECM

Function	Analyte Name	LOD (pg/mg)	Unprocessed Placenta Tissue (n = 3) ^a Avg (pg/mg)	Processed ECM (n = 4) ^a Avg (pg/mg)
Growth Factors and other regulators of wound healing, scarring and fibrosis	Platelet Derived Growth Factor-AA (PDGF-AA)	3.90	<LOD	<LOD
	Platelet Derived Growth Factor-BB (PDGF-BB)	3.90	6.38	ND
	Basic Fibroblast Growth Factor beta (β FGF)	7.82	230.32	ND
	Epidermal Growth Factor (EGF)	3.90	<LOD	ND
	Transforming Growth Factor beta 1 (TGF- β 1)	7.82	ND	ND
	Hepatocyte Growth Factor (HGF)	7.82	2592.48	ND
	Placental Growth Factor (PLGF)	0.39	47.27	<LOD
	Vascular Endothelial Growth Factor (VEGF)	7.82	ND	ND
	Insulin Like Growth Factor-1 (IGF-1)	142.40	ND	ND
	Growth and Differentiation Factor-15 (GDF-15)	0.98	1675.49	<LOD
	Intercellular Adhesion Molecule-one (ICAM-1)	136.80	483.37	ND
Anti-inflammatory	Interleukin-10 (IL-10)	3.90	ND	ND
	Interleukin-1 Receptor Antagonist (IL-1RA)	3.90	11.55	ND
	Interleukin-6 (IL-6)	3.90	8.22	ND

Function	Analyte Name	LOD (pg/mg)	Unprocessed Placenta Tissue (n = 3) ^a Avg (pg/mg)	Processed ECM (n = 4) ^a Avg (pg/mg)
Pro-inflammatory	Granulocyte Macrophage-Colony Stimulating Factor (GM- CSF)	3.90	ND	ND
	Interleukin-12p40 subunit (IL-12p40)	3.90	ND	ND
	Interleukin-1 beta (IL-1 β)	3.90	<LOD	ND
	Interleukin-5 (IL-5)	3.90	ND	ND
	Interleukin-8 (IL-8)	4.30	17.68	ND
	Interleukin-13 (IL-13)	3.90	ND	ND
	Interleukin-15 (IL-15)	3.90	3.91	ND
	Monocyte Chemoattractant Protein-1 (MCP-1)	3.90	15.12	ND
	Macrophage Inflammatory Protein-1 alpha (MIP-1 α)	3.90	ND	ND
	Macrophage Inflammatory Protein-1 beta (MIP-1 β)	3.90	5.57	ND
	Regulated on Activation, Normal T Expressed and Secreted (RANTES)	3.90	34.89	<LOD
	Tumor Necrosis Factor Alpha (TNF α)	3.90	<LOD	ND

^a 4 lots of ECM were tested to obtain the statistic, compared to average of 3 unprocessed placenta tissue samples

^b Reported as ND, although one of four samples showed far below standard curve signal, which is considered outlier based on the facts that the results of all unprocessed placenta and ECM samples are ND.

LOD: Limit of Detection; ND: Not Detected; Avg: Average

[0097] Moreover, the presence of any hormones such as Human Chorionic Gonadotropin (hCG), Follicle-stimulating Hormone (FSH), Lactogen, Estrogen, Progesterone and Oxytocin in the postpartum unprocessed placenta and final ECM were also evaluated. The results showed these hormones were detected in the unprocessed placenta however were below the limit of detection (LOD) or not detectable (ND) in the processed ECM (see Table 4).

Table 4

Hormone Quantification in Processed ECM Compared to Unprocessed Placenta

Hormone Name	Biochemistry	LOD (ng/mg)	Unprocessed Placenta (n = 3) Avg (ng/mg)	Processed ECM (n = 3) Avg (ng/mg)
Human Chorionic Gonadotropin (HCG)	Peptide	0.001	0.046 ± 0.055	ND
Follicle-Stimulating Hormone (FSH)	89 - 112aa peptide	0.002	<LOD	<LOD
Lactogen	Peptide	0.8	491 ± 17.2	ND
Estrogen	Chemical	0.0003	0.004 ± 0.001	<LOD
Progesterone	Chemical	0.001	0.760 ± 0.240	ND
Oxytocin	9-mer peptide	0.0003	0.0004 ± 0.0003	<LOD

Example 5: Histology

[0098] The absence of residual cells and cell debris was demonstrated by using a standard Hematoxylin and Eosin (H&E) staining assay. As depicted in Figure 5A and 5B, cells, or nuclear material (dark blue) are clearly observed in fresh unprocessed placenta tissue.

[0099] The processed ECM (FIG. 6A) was compared to unprocessed placenta (FIG. 6B) following the manufacturing steps, including osmotic shock, detergent treatment as well as an acid/base step, was substantially free of cell Debris

[0100] The presence of DNA in SDPECTM compositions was analyzed using agarose gel electrophoresis. Extracted native placental tissue samples showed presence of DNA as well as degraded fragments that are in low molecular size, while samples extracted from SDPECTM compositions of four separate lots showed no presence of any residual DNA or fragments in the size range of below 200bp (Figure 7) indicating complete removal of any DNA residual from the product.

Example 6: Mesenchymal Stem Cell Attachment and Growth on SDPECTM of the Present Disclosure

[0101] Human mesenchymal stem cells were seeded on SDPECTM pharmaceutical compositions of the present disclosure, and their attachment and growth was documented. The hypothesis is that a purified, native form of connective tissue matrix will support cell attachment and growth.

[0102] The cells were seeded on improved placental high concentrations (e.g. 5mg/well in a 48 well plate, each well 1 ml volume) and low concentrations (e.g. 2.5 mg/well in a 48 well

plate, each well 1 ml volume) of SDPECTM compositions and allowed to proliferate in comparison to an SDPECTM alone. PrestoBlue assay showed increased proliferation of cells from day 1 to day 7 (Figure 8A). Calcein AM staining showed both high and low concentration of an SDPECTM of the present disclosure supports higher cellular viability compared to TCP in absence of serum (Figure 8B).

Example 7: Human Tenocyte Attachment and Growth on Crosslinked Purified Bovine Collagen Scaffolds

[0103] Attachment and growth of cell was tested by culturing the Tenocytes on tissue culture plates that were coated with purified bovine collagen product. Poor growth of cells was observed as seen from Calcein staining, as shown in Figure 9. When compared to SDPECTM of the present disclosure, the results indicate an SDPECTM of the present disclosure is superior and favorable for cell growth and attachment.

Example 8: ATR-FTIR Analysis of Collagen Stability in an SDPECTM of the Present Disclosure

[0104] To test collagen stability, Fourier-transform infrared spectroscopy (FTIR) in Attenuated Total Reflectance (ATR) mode, was utilized. FTIR spectra of an SDPECTM of the present disclosure were analyzed in triplicate using Thermo Fisher Nicolet iS10 (Thermo Fisher, Waltham, MA). Collagen degradation often involves matrix, changes in the molecular structure, resulting in the formation of new chemical groups or altered functional groups. ATR-FTIR can detect these changes and provide valuable information about the degradation process.

[0105] A placenta type I collagen standard was used as a control for the organic phase. Spectra were acquired in a reflectance mode, between the range of 4000 and 400 cm^{-1} , averaging a minimum of five scans. The spectra represent the intensity of the absorbed light at different wavenumbers. The analysis of the collagen stability was assessed based on the ATR-FTIR spectra with the typical amide peaks of collagen present at time 0 and compared to different time points.

[0106] Data processing was performed using OMNIC software. The obtained ATR-FTIR spectra were analyzed to identify characteristic absorption peaks associated with collagen degradation products. Changes in peak intensities, shifts in peak positions, or the appearance of new peaks provide insights into the degradation process and the formation of collagen degradation products. Additionally, structural analysis about various functional groups in collagen, such as amide bands (I, II, and III), which are associated with the peptide backbone, were

performed. Changes in the amide bands, such as shifts or broadening, can indicate structural modifications in collagen due to degradation.

Example 8: The use of an SDPECTM of the present Disclosure for Maintenance of Donor Sites/Grafts Associated with Hair Transplantation

- [0107]** A placenta type I collagen standard was used as a control for the organic phase. Spectra were acquired in a reflectance mode, between the range of 4000 and 400 cm^{-1} , averaging a minimum of five scans. The spectra represent the intensity of the absorbed light at different wavenumbers. The analysis of the collagen stability was assessed based on the ATR-FTIR spectra with the typical amide peaks of collagen present at time 0 and compared to different time points.
- [0108]** Follicular Unit Extraction (FUE) and Follicular Unit Transplantation (FUT) are two widely used techniques for hair transplantation, each with their unique approach and benefits.
- [0109]** Follicular Unit Extraction (FUE) is a minimally invasive procedure that involves the extraction of individual hair follicles from the donor area using specialized microsurgical tools or a robot. Each hair follicle is extracted one by one, typically from the back or sides of the scalp, where hair growth is genetically resistant to balding. These follicles are then meticulously transplanted into the recipient area, where hair loss has occurred.
- [0110]** On the other hand, Follicular Unit Transplantation (FUT), also known as strip harvesting, involves the surgical removal of a strip of scalp tissue from the donor area. The tissue strip is then dissected into individual follicular units under a microscope before being transplanted into the recipient area. FUT allows for the transplantation of a larger number of grafts in a single session, making it suitable for patients requiring extensive hair restoration.
- [0111]** After a hair transplant procedure, the wound healing process plays a crucial role in the successful growth and integration of transplanted hair follicles. Immediately after the hair transplant, the recipient area will have small incisions or punctures where the hair follicles were inserted. The body initiates the first stage of wound healing, known as the inflammatory phase. This phase involves the release of immune cells, growth factors, and other substances that promote healing.
- [0112]** In the following days and weeks, the second stage, known as the proliferative phase, begins. During this phase, the body produces new blood vessels to supply oxygen and nutrients to the transplanted follicles. The transplanted hair grafts establish a blood supply connection with the surrounding tissue, facilitating their survival and growth. Scabbing and crusting around the transplanted area will occur.

[0113] The final stage of wound healing is the remodeling phase, which can last several months. During this stage, the newly transplanted hair follicles gradually settle into their new location and start to grow new hair. The use of an SDPECTM of the present disclosure during hair grafting procedure will provide the necessary maintenance of the donor and recipient site.

Example 9: Formulations of an SDPECTM of the Present Disclosure For Wound Management

[0114] SDPECTM compositions disclosed herein are formulated into a particulate form for ease of injection or for topical administration. The formulation is stable at room temperature.

[0115] SDPECTM compositions as disclosed herein are supplemented with the additional constituents selected from a group consisting of placental-derived ingredients including but not limited to placental cells such as mesenchymal-like stromal adherent cells (MLASCs), MLASCs conditioned media, MLASCs -derived micronutrients, placental exosomes, placental perfusate or placental plasma to provide additional benefits for wound management associated with various conditions including but not limited to partial- and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled / undermined wounds, surgical wounds (donor sites/grafts, during hair transplantation, post Mohs surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, and skin tears), draining wounds and partial-thickness burns.

Example 10: Clinical Study of an SDPECTM of the present Disclosure for Wound Management During Hair Transplantation

[0116] The objective of this study will be to determine the potential of compositions of an SDPECTM disclosed herein for wound management during hair transplantation. The following study considerations will be addressed:

Study duration

Study endpoints

Dosing of an SDPECTM of the Disclosure.

[0117] The following key benefits of an SDPECTM compositions disclosed herein will be expected:

Management of wound healing associated with hair transplantation procedure.

Wound management of the graft and recipient site

Extension of the survival rate of grafts.

Improved the healing rate of transplanted hair follicle units, thereby increasing the survival rate of transplanted hair grafts.

Improved donor area healing at the back of the head from follicular unit transplantation (FUT), or follicular unit extraction (FUE) procedures.

- [0118]** A total of 25 male and female subjects, ranging in age from 19 to 63 years who met all the inclusion criteria and had none of the exclusion criteria, as outlined in the clinical study protocol, will be selected for study participation.
- [0119]** The study will enroll 25 male patients. Inclusion criteria included 19–63 years; MPHL from stage IIa to stage IV according to the Norwood-Hamilton classification (Table 1); and the participant will be considered suitable for placental derived ECM injection from a surgical point of view as assessed by the expected cosmetic results and the transfusional service. Exclusion criteria will be divided into two types: local and systemic. The systemic criteria included platelets disorders, thrombocytopenia, antiaggregating therapy, systemic treatments for MPHL (such as finasteride, dutasteride, and antiandrogens) in the previous 12 months, bone marrow aplasia, uncompensated. The local criteria will include MPHL stages V–VII, topical treatments for MPHL (e.g., minoxidil, prostaglandin, analogs, retinoids, and corticosteroids) in the previous 12 months, and withdrawal of informed consent. Patients with a propensity for keloids and patients who were immunosuppressed will be excluded.
- [0120]** All participants included will be assessed by two experts in plastic surgery. The allocation sequence will be generated using an online randomization generator and will be concealed by a person unrelated to the trial management group. The participants, study personnel, and outcome assessors will all be blinded to treatment allocation, and blinding will be maintained until all data has been analyzed.
- [0121]** All participants included will be assessed by two experts in plastic surgery. The allocation sequence will be generated using an online randomization generator and will be concealed by a person unrelated to the trial management group. The participants, study personnel, and outcome assessors will all be blinded to treatment allocation, and blinding will be maintained until all data has been analyzed.
- [0122]** All participants included will be assessed by two experts in plastic surgery. The allocation sequence will be generated using an online randomization generator and will be concealed by a person unrelated to the trial management group. The participants, study personnel, and outcome assessors will all be blinded to treatment allocation, and blinding will be maintained until all data has been analyzed.
- [0123]** The primary outcome will be residual hair count and hair density based on computerized trichogram. The secondary outcomes will be microscopic evaluation (Fig. 2) of the epidermis thickness in placental derived ECM-treated hair skin and increase in the number of follicles compared with baseline value and evaluation of safety and feasibility. The safety

and clinical efficacy of SDPECTM injections for wound management associated with hair transplantation as a treatment for pattern hair loss will be investigated. A disclosed SDPECTM will be injected on half of the selected patients' scalps with pattern hair loss. The other half will be treated with placebo. One treatment will be administered to each patient. The endpoints will include hair regrowth, hair dystrophy as measured by dermoscopy, burning or itching sensation, and cell proliferation as measured by Ki67 evaluation.

[0124] Patients will be followed for 1 year. At the end of the treatment cycle, the patients will be observed for clinical improvement in the mean number of hairs, with a mean increase of hairs in the target area, and a mean increase in total hair density of hairs per cm² compared with baseline values. Any potential side effects will be noted during treatment. Microscopic evaluation will be employed to assess the increase of epidermis thickness and the number of hair follicles 2 weeks after the SDPECTM treatment compared with baseline value ($p < .05$ will indicate statistical significance).

[0125] Also, an increase of Ki67+ keratinocytes in the epidermis and of hair follicular bulge cells will be documented, and an increase of small blood vessels around hair follicles in the treated skin compared with baseline ($p < .05$).

[0126] Relapse of androgenic alopecia will not be evaluated in patients until 12 months after the treatment. In case patients report progressive hair loss, which might be evident 16 months after the treatment, those patients will be re-treated.

[0127] The collected data will clearly highlight the positive effects of SDPECTM injections in male pattern hair loss and absence of major side effects and might be a safe and effective treatment option against hair loss.

Example 10: Isolation and Purification of Placental Exosomes (pExo) from Human Placenta

[0128] Full-term human placentas were procured through donors with full consent. The placentas are processed into small tissue fragments by dissection and placed in sterile cell culture containers such as roller bottle bioreactors filled with sterile saline solution. The placenta tissues are incubated at room-temperature or defined cultured conditions such as incubators for at least 2 hours and then the supernatant of the tissue-culture is isolated with centrifugation. The supernatants centrifuged with two step centrifugations: first step is at 3000g and second step is at 10,000g to obtain a supernatant of pExo for ultra-centrifugation. The supernatant from the 10,000g centrifuge (S10,000g) is then used for ultra-centrifugation at 100,000g in which the supernatant is discarded, and the pellet retained. The pellet is then resuspended in solutions such as PBS, saline, and used as constituent of a disclosed SDPECTM composition.

[0129] Protein concentration of pExo is quantified with BCA protein assay method. The size is determined by NanoSight. The cytokine composition of pExo is measured with MILLIPEX-MAP human cytokine/chemokine-PX41.

Example 11: Placental Mesenchymal-like Adherent Stromal Cells (MLASCs) Population-Derived Cell Supernatants and Micronutrients

[0130] Placental MLASCs were isolated from normal, full-term human placental tissue. Cells are culture expanded as a plastic-adherent undifferentiated in vitro population. MLASCs are $\geq 95\%$ CD34-, CD10+, CD105+ and $\geq 84\%$ of the cells as CD200+. The remaining cells are part of the same continuous population but are not considered positive by flow cytometry because their signal is too weak. Cells are roughly spherical in mono-dispersed suspension with an average cell diameter of $19 \pm 1 \mu\text{m}$.

[0131] The cells have the genetic make-up of the baby, not the mother. When cells are cultured for over 24 hours, cell micronutrients are collected and used as one of components of an SDPECTM composition disclosed herein. Physical embodiments of the cell micronutrients include, but are not limited to, liquid or solid, frozen, lyophilized or dried into a powder. Cell micronutrients contain many of the original components of the medium, as well as a variety of cellular metabolites and secreted proteins, including, for example, biologically active growth factors, anti-inflammatory mediators, and secreted extracellular matrix proteins. Micronutrients are used as one of the constituents of an SDPECTM composition disclosed herein.

Example 11: Placental Perfusate Serum and Cord Blood Serum

[0132] Placental tissue is cannulated and perfused under aseptic conditions with saline. Umbilical cord blood obtained from cord collection is also used to extract serum from cord blood. Both placental perfusate and cord blood are subjected to plasma extractor to remove any cellular components WBC, RBC etc. The plasma is further subjected to low-speed centrifugation to further remove any residual cells and platelets. Plasma from both placental perfusate and cord blood are subjected to series of filtration steps to remove further impurities in serum purification process. 0.2-micron filter to remove large cellular debris, 0.1-micron filter to remove endotoxin followed by hemoglobin based affinity purification for removal of free hemoglobin, followed by filters to remove large proteins such as fibrinogen, followed by Q and E filters to remove free DNA and endotoxin. The serum from placental perfusate or plasma from cord blood can be utilized as constituents of a disclosed SDPECTM. The residual growth factors and cytokines, including but not limited to PGE2, implicated in hair regrowth,

that are present in the placental serum or cord blood plasma are beneficial for wound management process and could be used in various forms, such as lyophilized powder, liquid or various ratios and combinations in the formulation as a constituent of a disclosed SDPECTM.

Example 12: An SDPECTM of the Present Disclosure Tested to Fill Defects in the Dermis or Subcutis

- [0133]** Collagen is a natural protein found in the skin that provides structure and elasticity. Dermal fillers based on human collagen are designed to replenish and augment the skin's collagen levels, thereby reducing the appearance of wrinkles and adding volume to specific areas of the face. These fillers are typically derived from purified human collagen extracted from donor skin or tissue.
- [0134]** Dermal fillers are injectable substances used to add volume, smooth wrinkles, and restore youthful contours to the face. They work by plumping up the targeted area, filling in lines and wrinkles, and enhancing facial features. The most commonly used dermal fillers are made from various materials, such as hyaluronic acid, collagen, calcium hydroxyapatite, and poly-L-lactic acid. These fillers all have drawbacks, as their plumping effect might not look natural and will diminish with time.
- [0135]** Since an SDPECTM of the present disclosure is composed of predominantly collagen and additional minor component, elastin, which are developmentally early stage, they might stimulate the body's natural collagen production over time. This helps to improve the results gradually and gives a more natural-looking outcome and more durability as the body regulates collagen production.
- [0136]** This study evaluated the SDPECTM compositions for persistence and local tissue response following implantation of 41.7mg in 0.2ml subcutaneously in Sprague-Dawley rats. SDPECTM of the present disclosure, both crosslinked and non-crosslinked versions, with particle sizes including: $\leq 1000 \mu\text{m}$, or $\leq 300 \mu\text{m}$ or $\leq 200 \mu\text{m}$. were subcutaneously injected as either a bleb or linear line along the dorsal surface of the animal using a 25G needle. Immediately post implantation and every 10 days thereafter, the volume of the injection site was measured as $(\text{height} \times \text{diameter} \times \text{diameter})/2$ for bleb injections and $\text{length} \times \text{height} \times \text{width}$ for linear injections. At 2, 4, 8, 16, 20, and 26 weeks, 2 rats per timepoint were sacrificed and the implant site was evaluated histologically.
- [0137]** The histology evaluation focused on the local tissue response which demonstrated a decrease in the immune response over time until steady state was achieved by either week 4 or week 8 depending on the formulation of the SDPECTM composition implanted. Persistence at week 2 showed that the implant was essentially absorbed ($\leq 10\%$ of the implanted material

remains extracellular) at all the implant sites. For the remainder of the study out to week 26, most of the implant sites showed complete absorption of the test articles (no implanted material remained extracellular; test material was visible within cells at the implant site).

[0138] As an SDPECTM of the present disclosure is within the cells (Figure 13, black arrows), that might stimulate the body's natural/endogenous collagen production over time. This mechanism of action might help to improve the results gradually and give a more natural-looking outcome and more durability as the body regulates collagen production over time.

Example 13: The Use of an SDPECTM of the Present Disclosure for Wound management post Laser Surfacing

[0139] Laser resurfacing produces a controlled skin injury, resulting in a wound healing response. This wound healing response allows for collagen remodeling, which improves skin texture and tone. Topical agents are often employed following laser treatments to facilitate recovery. The introduction of an SDPECTM of the present Disclosure allows for recovery post laser treatment.

[0140] This study will be performed to assess the safety and effectiveness of an SDPECTM of the present disclosure following laser resurfacing. Ablative laser resurfacing utilizing carbon dioxide (CO₂) and erbium-doped yttrium aluminum garnet (Er:YAG) lasers targets water in tissue, causing vaporization of the entire epidermis and varying levels of the dermis. The subsequent healing response results in structural rejuvenation, improving texture and tone. Depending on the degree of controlled injury, the healing process usually lasts several days to several weeks. There are three broad stages of the wound healing process post laser resurfacing: inflammatory, proliferative, and remodeling. The inflammatory stage involves the influx of leukocytes to the wound, leading to erythema, edema, and coagulation. Additionally, macrophages migrate to the wound to initiate the formation of granulation tissue. The proliferative stage starts at 48 hours and is characterized by vascular remodeling and angiogenesis. The remodeling phase, which begins two to three weeks after the initial wound, consists of resynthesis of the granulation tissue and the conversion of type III Collagen to type I Collagen, leading to increased strength of the forming scar⁸. In order to maximize the safety and efficacy of laser-resurfacing procedures, careful attention must be paid to postoperative wound care.

[0141] Postoperative wound management will be addressed by the use of an SDPECTM of the present disclosure. The SDPECTM will be hydrated in sterile saline solution at ratio of 100 mg SDPECTM hydrated with 1 ml sterile saline for not less than approximately 30 seconds and resulting paste is aspirated into a syringe and applied onto a surface of the wound (see Section

9). SDPECTM functions as a temporary wound cover which is slowly resorbed during the wound healing process.

[0142] The study will include 20 patients with a split-face treatment regimen with bilateral dermal melasma treated with fractional resurfacing followed by the application of a disclosed SDPECTM unilaterally. The outcome would be patient reported outcomes including reduction in pain, cutaneous dryness, and erythema on the SDPECTM side relative to the control side. The observations will be ranked, and a statistical significance will be reported at $p < 0.05$. Additionally, an investigator assessment will be performed ranking the following parameters including reduction of erythema on the treatment side, reduction of redness and cutaneous dryness. Overall reduction of adverse effects following laser-resurfacing will be reported based on the SDPECTM wound management post laser resurfacing.

Example 14: The Safety and Effectiveness of an SDPECTM of the Present Disclosure for Wound Management of Chronic, non-healing diabetic foot ulcers (DFUs)

[0143] The purpose of this study is to determine the safety and effectiveness of an SDPECTM disclosed herein for wound management of chronic, non-healing DFUs. The trial will include 30 completed subjects. The estimated enrollment period is 13 weeks. After completing a screening, the subjects will be enrolled and receive treatment followed for at least 12 weeks.

[0144] It is expected that the majority of the subjects will be recruited from patients being seen in the Investigators' practices. No minors will be included in the study and it is anticipated that there will be a roughly equal representation of male and female subjects. Further, no subjects will be excluded because of race or ethnicity and all efforts will be made to adequately represent the study population in the area in which they are chosen. All subjects will be used for the analysis of efficacy and safety data. Eligible subjects will be treated with a weekly application for 12 weeks of sterilized, SDPECTM compositions followed by standard of care wound therapy and offloading.

[0145] The primary endpoint measure will be wound healing area using digital image. The primary endpoint for the study is assessment of ulcer area at Weeks 6 and 12 using the MOLECULIGHT Imaging Device. The secondary outcome measure will be 1) wound closure - time to complete wound closure as defined by FDA and 2) Percentage area reduction - Rate of wound closure as assessed by wound area measurements determined by weekly percent area reduction. Adverse events as reported at weekly treatment visits. Other outcome measure will include 1) Reduction in bacterial burden as assessed by fluorescence imaging using the molecule imaging device at weeks 4, 8 and 12 and 2) Presence of protease levels - reduction in host proteases at weeks 4, 8, and 12.

Inclusion Criteria include:

[0146] Male or female patients over 18 years of age who have given written informed consent in accordance with the ICH Good Clinical Practice (GCP) guideline. Female subjects must be either of non-childbearing potential or if of childbearing potential must satisfy the defined contraceptive criteria Exclusion criteria h;

Patients who are willing and able to attend all follow up visits;

Subject has a known history of Type 1 or Type 2 diabetes with a HbA1c $\leq 12\%$.

Has a diabetic foot ulcer classified by the Wagner classification 1 or 2 and at least 0.75cm² and less than 5.0 cm² in surface area as determined by photographic planimetry at the time of enrollment;

[0147] Index ulcer characteristics:

Ulcer present for ≥ 30 days prior to (Day 0);

Index ulcer is located below the ankle: at least 50% of the ulcer surface area is below the malleolus;

Subject has Body Mass Index (BMI) ≤ 45 at enrollment.

Subject has adequate circulation to the affected extremity, as demonstrated by at least one of the following within the past 30 days:

Dorsum transcutaneous oxygen test (TcPO₂) with results ≥ 30 mmHg, ABIs with results of ≥ 0.7 and ≤ 1.2 ,

Doppler arterial waveforms, which are triphasic or biphasic at the ankle of the affected foot. For ABPI > 1.2 TBI (Toe Brachial Index) > 0.5 ,

Patient able to ambulate at home or in the clinic with or without mobility aids

The subject is willing to accept treatment with a porcine based product 9. The subject is medically stable, in the opinion of the investigator.

[0148] Exclusion Criteria:

1. Index Ulcer Assessment:

a. Penetrates down to muscle, tendon, or bone

b. Presence of another diabetic foot ulcer within 2 cm of the index ulcer

c. Index ulcer determined to be due to Active Charcot deformity or previous surgical correction for Charcot deformity.

d. Wounds which occur in relation to major structural abnormalities of the foot, which would include amputations related to osteomyelitis or Charcot deformity

- e. Exhibits overt clinical signs and symptoms of infection with cellulitis surrounding the wound margin.
 - f. Known or suspected local skin malignancy to the index diabetic ulcer
 - g. Wound duration > one year without intermittent closure
2. Prior therapies - Subjects receiving treatment with any of the following will not be eligible for enrollment:
- a. In the last 7 days - Negative pressure wound therapy (wound vac or SNAP) of the index ulcer
 - b. In the last 7 days - Hyperbaric oxygen (HBO) therapy
 - c. In the last 10 days - Chemical debridement, hypochlorous acid or Dakin's solution, medical honey therapy
 - d. In the last 30 days - Treatment with cytotoxic chemotherapy, application of topical steroids to the ulcer surface, or use of ≥ 14 days of immune-suppressants (including systemic corticosteroids); or subject is anticipated to require such medications during the course of the study
 - e. In the last 30 days - study ulcer treatment with any advanced therapy, including, biomedical or topical growth factors, tissue engineered materials (e.g. Apligraf or Dermagraft), sterilized placental allografts (EpiFix, NovaFix, etc.), or other scaffold materials (e.g. OASIS® Wound Matrix, MatriStem Wound Matrix)
 - f. In the last 30 days - Subject has been on any investigational drug(s) or therapeutic device(s)
 - g. In the last 8 weeks - Amputation or revascularization (surgical or stenting) to the affected leg.
3. Subject criteria that will make subject ineligible for enrollment:
- a. Known hypersensitivity to porcine based products
 - b. Known osteomyelitis or active cellulitis requiring antimicrobial therapy at wound site
 - c. End stage renal disease requiring dialysis.
 - d. Immune system disorders including Systemic Lupus Erythematosus (SLE), Acquired Immunodeficiency Syndrome (AIDS) or HIV

- e. Presence of any condition (including current drug or alcohol abuse, medical or psychiatric condition) that is likely to impair understanding of or compliance with the study protocol in the judgment of the Investigator
- f. Pregnancy at enrollment or within last 6 months, women who are breastfeeding, or women of childbearing potential who are planning to become pregnant during the time of the study OR are unwilling/unable to use acceptable methods of contraception (birth control pills, barriers, or abstinence)
- g. Subjects currently enrolled in this study. Concurrent enrollment in the study is prohibited
- h. Subjects currently receiving radiation therapy or chemotherapies
- i. Any pathology that would limit the blood supply and compromise healing or non-revascularizable surgical sites

[0149] The SDPECTM compositions are reconstituted in saline and applied onto wounds. Approximately 100mg of particulate SDPECTM can cover 50 cm² surface area.

[0150] The study will assess the ulcer area at Weeks 6 and 12. In addition, wound closure - time to complete wound closure (defined as 100% reepithelialization as determined by the investigator) as defined by FDA and 2) Percentage area reduction - Rate of wound closure as assessed by wound area measurements determined by weekly percent area reduction.

[0151] Adverse events will be reported at weekly treatment visits. Other outcome measures will include 1) Reduction in bacterial burden as assessed by fluorescence imaging using the moleculight imaging device at weeks 4, 8 and 12 and 2) Presence of protease levels - reduction in host proteases at weeks 4,8, and 12.

[0152] An SDPECTM composition disclosed herein is expected to serve as a wound cover and the same time to reduce the inflammatory response by shifting macrophages from M1 into M2 phenotype as well as provide a template for host cells to reepithelialize the wounds resulting in wound closure.

[0153] The present disclosure is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the disclosure in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A Sterile Decellularized Placental derived extracellular connective tissue matrix (SDPECTM) for use in wound management associated with a condition or disorder, comprising:
 - (a) greater than about 50% by weight placental derived collagen;
 - (b) greater than about 10% by weight elastin; and
 - (c) greater than about 10% moisture content,wherein the SDPECTM is substantially free of residual material.
2. The SDPECTM of Claim 1, further comprising:
 - (i) about less than 1% by weight:
 - (a) sulfated glycosaminoglycans;
 - (b) proteoglycans; or
 - (c) a mixture of (a) and (c);
 - (2) laminin; and
 - (3) fibronectin.
3. The SDPECTM of either of Claims 1 or 2, wherein the residual material is not quantifiable as being not detectable, or present at an amount less than the limit of detection.
4. The SDPECTM of any one of Claims 1-3, wherein the residual material comprises: (1) cells, (2) cell debris, (3) nucleic acid molecules, (4) nucleotides, (5) growth factors, (6) cytokines, (7) chemokines, (8) hormones, or (9) any combination of (1)-(8)
5. The SDPECTM of Claim 4, wherein the following chemokines, cytokines and growth factors are not detectable in the SDPECTM or are present in the SDPECTM at an amount less than the limit of detection:

- (a) Platelet Derived Growth Factor-AA (PDGF-AA), less than the limit of detection;
- (b) platelet Derived Growth Factor-BB (PDGF-BB), not detected;
- (c) Basic Fibroblast Growth Factor beta (β FGF), not detected;
- (d) Epidermal Growth Factor (EGF), not detected;
- (e) Transforming Growth Factor beta 1 (TGF- β 1), not detected;
- (f) Hepatocyte Growth Factor (HGF), not detected;
- (g) Placental growth Factor (PLGF), not detected;
- (h) Vascular Endothelial Growth Factor (VEGF), not detected;
- (i) Insulin Like Growth Factor-1 (IGF-1), not detected;
- (j) Growth and Differentiation Factor-15 (GDF-15), less than level of detection;
- (k) Intercellular Adhesion Molecule-1 (ICAM-1), not detected;
- (l) Interleukin-10 (IL-10), not detected;
- (m) Interleukin-1 Receptor Antagonist (IL-1RA), not detected;
- (n) Interleukin-6 (IL-6), not detected;
- (o) Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF), not detected;
- (p) Interleukin-12p40 subunit (IL-12p40), not detected;
- (q) Interleukin-1 beta (IL-1 β), not detected;
- (r) Interleukin-5 (IL-5), not detected;
- (s) Interleukin-8 (IL-8), not detected;
- (t) Interleukin-13 (IL-13), not detected;
- (u) Interleukin-15 (IL-15), not detected;
- (v) Monocyte Chemoattractant Protein-1 (MCP-1), not detected;
- (w) macrophage Inflammatory Protein-1 alpha (MIP-1 α), not detected;
- (x) Regulated on Activation, Normal T Expressed and Secreted (RANTES), less than the limit of detection;
- (y) Tumor Necrosis Factor alpha (TNF α), not detected;
- (z) Human Chorionic Gonadotropin (hCG), not detected;

- (aa) Follicle Stimulating Hormone (FSH), less than the level of detection;
- (bb) Lactogen, not detected;
- (cc) Estrogen, less than the limit of detection;
- (dd) Progesterone, not detected; and
- (ee) Oxytocin, less than the limit of detection

6. The SDPECTM of any one of Claims 1-5, wherein the DPECTM is in the form of particles.

7. The SDPECTM of any one of Claims 1-6, wherein the condition or disorder to which the wound management is associated with comprises:

- (a) partial thickness wounds;
- (b) full thickness wounds;
- (c) pressure ulcers;
- (d) venous ulcers;
- (e) diabetic ulcers;
- (f) vascular disorders;
- (g) tunneled wounds;
- (h) undermined wounds;
- (i) surgical wounds;
- (j) trauma wounds;
- (k) draining wounds; or
- (l) partial-thickness burns.

8. The SDPECTM of Claim 7, wherein:

- (a) the surgical wounds are wounds resulting from:

- (i) donor and graft sites from hair transplantation;
- (ii) post-Mohs surgery
- (iii) post-laser surgery;
- (iv) wounds from podiatric surgery; or
- (v) wound dehiscence; and

(b) the trauma wounds are wounds resulting from:

- (i) abrasions;
- (ii) lacerations; or
- (iii) skin tears.

9. A pharmaceutical composition for wound management comprising the SDPECTM of any one of Claims 1-8, and a pharmaceutically acceptable carrier.

10. The SDPECTM of any one of Claims 1-9 for use in a pharmaceutical composition for management wounds associated with a disease or condition in a subject in need thereof.

11. The use of Claim 10, wherein the condition or disorder with which the wound management is associated comprises:

- (a) partial thickness wounds;
- (b) full thickness wounds;
- (c) pressure ulcers;
- (d) venous ulcers;
- (e) diabetic ulcers;
- (f) vascular disorders;
- (g) tunneled wounds;

- (h) undermined wounds;
- (i) surgical wounds;
- (j) trauma wounds;
- (k) draining wounds; or
- (l) partial-thickness burns.

12. The use of Claim 13, wherein:

- (a) the surgical wounds are wounds resulting from:
 - (i) donor and graft sites from hair transplantation;
 - (ii) post-Mohs surgery
 - (iii) post-laser surgery;
 - (iv) wounds from podiatric surgery; or
 - (v) wound dehiscence; and
- (b) the trauma wounds are wounds resulting from:
 - (i) abrasions;
 - (ii) lacerations; or
 - (iii) skin tears

13. A method managing wounds associated with a disease or condition in a subject, comprising administering to the subject a therapeutically effective amount of the SDPECTM of any one of Claims 1-8, and the pharmaceutical composition of Claim 9.

14. The method of Claim 13, wherein administering the therapeutically effective amount of the SDPECTM comprises injecting the a pharmaceutical composition comprising the SDPECTM and an aqueous pharmaceutically acceptable carrier into a desired site in the subject.

15. The method of Claim 14, wherein the administration is subcutaneous administration.
16. The method of Claim 14, wherein administering the therapeutically effective amount of the SDPECTM comprises applying the SDPECTM topically to a desired site on the subject.
17. The method of any of Claims 13-16, further comprising the step of administering to the subject a therapeutically effective amount of a therapeutic agent.
18. The method of Claim 17, wherein the therapeutic agent comprises (a) a hyaluronic acid injection at the desired site, (b) a steroid injection at the desired site, (c) an opioid injection at the desired site, (d) a biologic injection at the desired site, or (e) an antibiotic.
19. The method of Claim 18, wherein the biologic comprises: (a) cells, (b) cell conditioned media, (c) exosomes, (d) plasma, (e) a nucleic acid molecule, (f) an antibody, (g) an anti-fungal agent, or (h) any combination of (a)-(g).
20. The method of Claim 19, wherein the nucleic acid molecule comprises DNA, RNA, mRNA, or siRNA, and the antibody comprises a fully human antibody, a humanized antibody, a single chain antibody (ScFv), or an active fragment of an antibody.
21. The method of any one of Claims 17-20, wherein the SDPECTM and the therapeutic agent are administered simultaneously, concomitantly, or serially.
22. A kit comprising one or more doses of the pharmaceutical composition of Claim 9.
23. The kit of Claim 22, further comprising an appropriately sized syringe for delivery of the dose(s) of the pharmaceutical composition, spraying or 3D printing.