

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

28 March 2019 (28.03.2019)



(10) International Publication Number

WO 2019/060355 A1

(51) International Patent Classification:

A61K 35/12 (2015.01) A61K 35/50 (2015.01)

A61K 35/48 (2015.01)

(21) International Application Number:

PCT/US2018/051651

(22) International Filing Date:

19 September 2018 (19.09.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

15/708,413 19 September 2017 (19.09.2017) US

15/708,425 19 September 2017 (19.09.2017) US

(72) Inventor; and

(71) Applicant: PETRUCCI, Gary, M. [US/US]; 2975 County Road 24, Long Lake, MN 55356 (US).

(74) Agent: WILLIS, Margaret, S., J. et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, MN 55440 (US).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: AMNION TISSUE PREPARATIONS AND METHODS OF USING

(57) Abstract: This document provides amnion tissue preparations (e.g., compositions including an amnion tissue preparation) and methods for using amnion tissue preparations. In some cases, amnion tissue preparations can be used for treating a mammal (e.g., a human) having one or more tumors. For example, embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) that can be used in arterial embolization to reduce or eliminate blood flow in a blood vessel that supplies a tumor are provided. In some cases, amnion tissue preparations can be used for treating a mammal (e.g., a human) having one or more wounds and/or skin disorders. For example, compositions including an amnion tissue preparation formulated for transdermal delivery that can be used to treat wounds and/or skin disorders are provided.



WO 2019/060355 A1

AMNION TISSUE PREPARATIONS AND METHODS OF USING

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Patent Application Serial No. 15/708,413, filed on September 19, 2017, and of U.S. Patent Application Serial No. 15/708,425, filed on September 19, 2017. The disclosures of the prior applications are
5 considered part of (and are incorporated by reference in) the disclosure of this application.

BACKGROUND

1. Technical Field

This document relates to amnion tissue preparations (e.g., compositions including
10 an amnion tissue preparation) and methods for using amnion tissue preparations. In some cases, amnion tissue preparations can be used for treating a mammal (e.g., a human) having one or more tumors. For example, embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can be used in arterial embolization to reduce and/or eliminate blood flow in a blood vessel that supplies a
15 tumor. In some cases, amnion tissue preparations can be used for treating a mammal (e.g., a human) having one or more wounds and/or skin disorders. For example, transdermal delivery of a composition including an amnion tissue preparation can be used to treat wounds and/or skin disorders.

2. Background Information

20 Cancer is among the leading causes of death in the United States and worldwide. In 2016, an estimated 1,685,210 new cases of cancer were diagnosed and 595,690 people died from the disease in the US alone (National Cancer Institute Cancer Statistics).

SUMMARY

This document provides methods and materials for treating a mammal (e.g., a
25 human) having one or more tumors. For example, embolic agents including an amnion tissue preparation (e.g., embolic agents coated with an amnion tissue preparation, also referred to as “amnion coated embolic agents”) provided herein can be used in arterial embolization to reduce and/or eliminate blood flow in a blood vessel that supplies a

tumor. In some cases, amnion coated embolic agents provided herein can be used to treat a mammal having one or more tumors.

Tumors cannot survive and grow without the oxygen and nutrients supplied by the vasculature. As described herein, reducing and/or eliminating blood flow in a blood vessel that supplies a tumor can deprive the tumor of the oxygen-carrying blood and other substances it needs to grow, thereby starving the tumor cells.

In general, one aspect of this document features a composition comprising an embolic agent having a coating including an amnion tissue preparation. The embolic agent can be a microparticle. The embolic agent can be a microsphere. The embolic agent can include a bio-compatible material. The bio-compatible material can be gelatin (e.g., tris-acryl gelatin), polyvinyl alcohol, ethylene vinyl alcohol copolymer, poly(lactic-co-glycolic acid), N-butyl-2 cyanoacrylate, collagen, thrombin, glue, calcium alginate, latex, silicon, starch, cellulose, chitosan, butyl cyanoacrylate, ethiodol, ethanol, ethanolamine oleate, sotradecol, or combinations thereof. The embolic agent can be resorbable. The embolic agent can be from about 0.5 μm to about 1200 μm in size. The amnion tissue preparation can include viable cells. The amnion tissue preparation can lack viable cells. The amnion tissue preparation can be a dried amnion tissue preparation (e.g., a dried amnion tissue preparation having a water content that is less than about 8 percent). The dried amnion tissue preparation can have a particle size ranging from about 0.1 μm to about 25 μm . The amnion tissue preparation can be the sole active ingredient. The embolic agent can be further coated with one or more therapeutic agents. The one or more therapeutic agents can include one or more angiogenesis inhibitors. The one or more therapeutic agents can include one or more chemotherapeutic agents. The one or more therapeutic agents can include one or more angiogenesis inhibitors and one or more chemotherapeutic agents.

In another aspect, this document features an artificial embolus comprising one or more compositions comprising an embolic agent having a coating including an amnion tissue preparation.

In another aspect, this document features a method for performing arterial embolization. The method includes, or consists essentially of, administering one or more compositions into a blood vessel of a mammal, where the composition includes an embolic agent having a coating including an amnion tissue preparation, where the one or more embolic agents form an embolus in the blood vessel, and where blood flow in the

blood vessel is reduced. The mammal can be a human. The composition does not induce an inflammatory response in the mammal.

In another aspect, this document features a method for treating a tumor in a mammal. The method includes, or consists essentially of, administering one or more compositions into a blood vessel of a mammal where the composition comprises an embolic agent having a coating including an amnion tissue preparation, where the one or more embolic agents form an embolus in the blood vessel, and where the size of the tumor is reduced. The tumor can be a benign tumor. The benign tumor can be a uterine fibroid. The benign tumor can be a benign prostatic hyperplasia. The tumor can be a cancerous tumor. The cancerous tumor can be a liver cancer tumor. The liver cancer can be a hepatocellular carcinoma, a cholangiocarcinoma, or a sarcoma. The cancerous tumor can be a kidney cancer tumor. The kidney cancer can be a renal cell carcinoma. The mammal can be a human. The composition does not induce an inflammatory response in the mammal.

This document also provides methods for transdermally administering a composition that includes an amnion tissue preparation and, optionally, a stem cell preparation. For example, a composition that includes an amnion tissue preparation and, optionally, a stem cell preparation can be administered transdermally as described herein to treat wounds (*e.g.*, a scar) and/or skin disorders (*e.g.*, psoriasis).

In general, one aspect of this document features a method for healing a wound in a mammal. The method includes, or consists essentially of, transdermally administering a composition including an amnion tissue preparation lacking viable cells to a mammal, where the size of the wound is reduced. The mammal can be a human. The wound can be an abrasion, an incision, a laceration, a puncture, an avulsion, or a burn. The wound can be a slow healing wound. The wound can be a scar. The size of the wound can be reduced by at least 5%. The transdermal administering can include iontophoresis. The iontophoresis can include from about 0.1 mA/cm² to about 1.0 mA/cm². The transdermal administering can include microinjection. The microinjection can include using a microneedle array. The transdermal administering can include a transdermal delivery device. The transdermal delivery device can be an adhesive patch. The amnion tissue preparation can include an amnion tissue preparation prepared from about 1 mg to about 10 g of amnion tissue. The composition also can include a stem cell preparation having viable cells, where the stem cell preparation includes from about 0.3 million to about 3

million stem cells. The amnion tissue preparation can be a human amnion tissue preparation. The stem cell preparation can be a human mesenchymal stem cell preparation.

In another aspect, this document features a method for treating a skin disorder in a mammal. The method includes, or consists essentially of, transdermally administering a composition including an amnion tissue preparation lacking viable cells to the mammal, where a symptom of the skin disorder is reduced. The mammal can be a human. The skin disorder can be eczema, psoriasis, rosacea, seborrheic dermatitis, acne, cold sores, shingles, basal cell carcinoma, squamous cell carcinoma, melanoma, actinic keratosis, vitiligo, melasma, or lentigenes. The skin disorder can be psoriasis. The symptom can be eliminated. The transdermal administering can include iontophoresis. The method iontophoresis can include from about 0.1 mA/cm² to about 1.0 mA/cm². The transdermal administering can include microinjection. The microinjection can include using a microneedle array. The transdermal administering can include a transdermal delivery device. The transdermal delivery device can be an adhesive patch. The amnion tissue preparation can include an amnion tissue preparation prepared from about 1 mg to about 10 g of amnion tissue. The composition also can include a stem cell preparation having viable cells, where the stem cell preparation includes from about 0.3 million to about 3 million stem cells. The amnion tissue preparation can be a human amnion tissue preparation. The stem cell preparation can be a human mesenchymal stem cell preparation.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DETAILED DESCRIPTION

This document provides amnion tissue preparations (e.g., compositions including an amnion tissue preparation) and methods for using amnion tissue preparations. In some cases, amnion tissue preparations can be used for treating a mammal (e.g., a human) having one or more tumors. For example, embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can be used in arterial embolization to reduce and/or eliminate blood flow in a blood vessel that supplies a tumor. In some cases, amnion tissue preparations can be used for treating a mammal (e.g., a human) having one or more wounds and/or skin disorders. For example, transdermal delivery of a composition including an amnion tissue preparation can be used to treat wounds and/or skin disorders.

The term “amnion tissue preparation” as used herein refers to a preparation of amnion tissue or amnion material. In some cases, an amnion tissue preparation can be a liquid preparation (e.g., solution or suspension) that is prepared from a dried amnion tissue preparation. The term “dried amnion tissue preparation” as used herein refers to a preparation of amnion tissue or amnion material that is dried to have a water content that is less than about 8 percent (e.g., less than about 7 percent, less than about 6 percent, less than about 5 percent, less than about 4 percent, less than about 3 percent, less than about 2 percent, or less than about 1 percent). In some cases, a dried amnion tissue preparation can have a water content that is between about 0.1 percent and about 8 percent (e.g., between about 0.5 percent and about 8 percent, between about 1 percent and about 8 percent, between about 0.1 percent and about 5 percent, between about 0.1 percent and about 4 percent, between about 0.1 percent and about 3 percent, between about 0.5 percent and about 5 percent, or between about 1 percent and about 4 percent).

An amnion tissue preparation can be dried using any appropriate technique such as micronization, vacuum drying, spray drying, freeze drying, or combinations thereof. In some cases, an amnion tissue preparation can be dried as described elsewhere (e.g., U.S. Patent No. 5,656,498). A dried amnion tissue preparation can have any appropriate particle size. For example, a dried amnion tissue preparation can have a particle size ranging from about 0.1 μm to about 25 μm (e.g., from about 0.5 μm to about 25 μm , from about 0.75 μm to about 25 μm , from about 1 μm to about 25 μm , from about 0.1 μm to about 15 μm , from about 0.1 μm to about 10 μm , from about 0.1 μm to about 7.5 μm ,

from about 0.1 μm to about 5 μm , from about 0.75 μm to about 7.5 μm , or from about 1 μm to about 5 μm).

An amnion tissue preparation or a dried amnion tissue preparation can contain viable cells, non-viable cells, or a combination thereof. For example, an amnion tissue preparation or a dried amnion tissue preparation can be a preparation of amnion tissue or amnion material having viable cells. In some cases, an amnion tissue preparation can be a solution or suspension of amnion tissue or amnion material having viable cells.

In some cases, an amnion tissue preparation or a dried amnion tissue preparation can be a preparation of amnion tissue or amnion material where all the cells were removed, killed, or lysed such that the amnion tissue preparation or the dried amnion tissue preparation lacks viable cells. In some cases, an amnion tissue preparation or a dried amnion tissue preparation can be a preparation of amnion tissue or amnion material that was exposed to one or more physical and/or chemical treatments that killed, fixed, or lysed the cells of the amnion tissue or amnion material such that the amnion tissue preparation or the dried amnion tissue preparation lacks viable cells. For example, temperature (e.g., rapid freezing or rapid freezing-thawing), force and pressure, and/or electrical disruption can be used to kill or lyse cells within amnion tissue or amnion material to produce an amnion tissue preparation or a dried amnion tissue preparation that lacks viable cells.

In some cases, amnion tissue or amnion material can be obtained and then treated in a manner designed to lyse all the cells within the amnion tissue or amnion material. In these cases, the resulting material (e.g., matrix material and cellular remnants from lysed cells) can be used as an amnion tissue preparation that lacks viable cells or dried to form a dried amnion tissue preparation that lacks viable cells.

In some cases, an amnion tissue preparation or a dried amnion tissue preparation can be prepared from human amnion tissue. For example, human amnion tissue can be harvested, processed to maintain cell viability with or without removing blood, and used as an amnion tissue preparation or dried to form a dried amnion tissue preparation.

In some cases, human amnion tissue can be processed to remove blood prior to being used as an amnion tissue preparation or prior to being dried to form a dried amnion tissue preparation. In some cases, human amnion tissue can be processed without removing cells or blood prior to forming an amnion tissue preparation or a dried amnion tissue preparation.

An example of an amnion tissue preparation includes, without limitation, a human amnion tissue preparation that includes viable cells. In some cases, an amnion tissue preparation can be obtained from MiMedX® or a tissue bank (e.g., a human tissue bank).

In some cases, an amnion tissue preparation or a dried amnion tissue preparation
5 can include a stem cell preparation. A stem cell preparation can be any appropriate stem cell preparation. The term “stem cell preparation” as used herein refers to a preparation of stem cells or stem cell material. In some cases, a stem cell preparation can be a liquid preparation (e.g., solution or suspension).

A stem cell preparation can contain viable stem cells, non-viable stem cells, or a
10 combination thereof. For example, a stem cell preparation can be a preparation of viable stem cells. In some cases, a stem cell preparation can be a solution or suspension of viable stem cells.

In some cases, a stem cell preparation can be a preparation of stem cell or stem cell material where all the stem cells were killed, fixed, or lysed such that the stem cell
15 preparation lacks viable stem cells. In some cases, a stem cell preparation can be a preparation of stem cells or stem cell material that was exposed to one or more physical and/or chemical treatments that killed, fixed, or lysed the stem cells such that the stem cell preparation lacks viable stem cells. For example, temperature (e.g., rapid freezing or rapid freezing-thawing), force and pressure, and/or electrical disruption can be used to kill
20 or lyse stem cells to produce a stem cell preparation that lacks viable stem cells.

In some cases, a stem cell culture can be obtained and then used as a stem cell preparation in a manner that maintains stem cell viability.

Examples of stem cell preparations include, without limitation, a mesenchymal stem cell (MSC) preparation (e.g., a MSC preparation obtained from fat tissue or bone
25 marrow), a neural stem cell (NSC) preparation (e.g., a NSC preparation obtained from a brain tissue such as striatum), an umbilical cord blood stem cell preparation, an embryonic stem cell preparation, and a human induced pluripotent stem cell preparation.

In some cases, stem cell preparations can be prepared from cultures of stem cells. For example, a culture containing from about 25 million to about 25 billion (e.g., from
30 about 25 million to about 20 billion, from about 25 million to about 15 billion, from about 25 million to about 10 billion, from about 25 million to about 5 billion, from about 25 million to about 1 billion, from about 50 million to about 25 billion, from about 75 million to about 25 billion, from about 100 million to about 25 billion, from about 150

million to about 25 billion, from about 250 million to about 25 billion, from about 500 million to about 25 billion, from about 50 million to about 20 billion, from about 75 million to about 15 billion, from about 100 million to about 10 billion, from about 150 million to about 5 billion, from about 250 million to about 2 billion, or from about 500 million to about 1 billion) stem cells can be used to make a stem cell preparation.

In some cases, a stem cell preparation can be obtained commercially from a variety of suppliers such as Stemedica Cell Technologies, Inc.

In some cases, an amnion tissue preparation and a stem cell preparation can be formulated into a single solution or suspension for administration to a mammal. For example, a dried amnion tissue preparation can be reconstituted into a solution and a stem cell preparation can be added to that solution to form a single solution or suspension having both an amnion tissue preparation and a stem cell preparation.

In some cases, an amnion tissue preparation also can include one or more therapeutic agents, one or more immunosuppressant agents (e.g., corticosteroids (e.g., corticosteroids such as glucocorticoids), cytostatics, antibodies, calcineurin inhibitors, and interferons), one or more anti-inflammatory agents (e.g., non-steroidal anti-inflammatory drugs, dexamethasone, or other type of glucocorticoid steroids), one or more growth factors (e.g., platelet derived growth factor (PDGF), epithelial growth factor (EGF), fibroblast growth factor-2 (FGF2), or stem cell factor (SCF)), and/or one or more antimicrobial agents (e.g., antibiotics such as kanamycin, neomycin, streptomycin, or gentamicin, or an antifungal agent).

In some cases, an amnion tissue preparation can be formulated for delivery to one or more blood vessels. For example, this document provides embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents), as well as methods and materials for making and using embolic agents including an amnion tissue preparation. For example, one or more amnion coated embolic agents (e.g., embolic agents coated with an amnion tissue preparation) provided herein can be used in arterial embolization to form one or more emboli (e.g., artificial emboli) that reduce and/or eliminate blood flow in a blood vessel. In some cases, one or more amnion coated embolic agents provided herein can be used to treat a mammal (e.g., a human) having one or more tumors. For example, one or more amnion coated embolic agents provided herein can be administered to a mammal to reduce and/or eliminate blood flow in a blood vessel that supplies a tumor in a mammal. In some cases, an amnion coated embolic agent can be used to deliver an

amnion tissue preparation to a blood vessel (e.g., to promote healing in the blood vessel). Also provided herein are artificial emboli formed from one or more (e.g., one, two, three, four, five, six, seven, eight, nine, ten, or more) amnion coated embolic agents provided herein.

5 Any appropriate embolic agent can include (e.g., be coated with) an amnion tissue preparation (e.g., human amnion tissue preparation) as described herein. An embolic agent can be in the form of a gel, a liquid, or a particle (e.g., a nanoparticle, a microparticle, or a macroparticle). In some cases, an embolic agent can be designed to change forms (e.g., to be delivered as a liquid and form a gel or a particle within a blood
10 vessel). An embolic agent that is a particle can be any appropriate shape (e.g., a sphere or a disk). In some cases, an embolic agent can be permanent (e.g., non-resorbable). In some cases, an embolic agent can be temporary (e.g., resorbable or dissolvable). Examples of embolic agents include, without limitation, beads (e.g., microspheres), plugs, foams (e.g., gelfoams), coils, and sponges. An embolic agent can include any appropriate
15 material (e.g., a bio-compatible material). Examples of materials that can be used for an embolic agent include, without limitation, gelatin (e.g., tris-acryl gelatin), polyvinyl alcohol, ethylene vinyl alcohol copolymer, poly(lactic-co-glycolic acid), N-butyl-2 cyanoacrylate, collagen, thrombin, glue, calcium alginate, latex, silicon, starch, cellulose (e.g., carboxymethyl cellulose), chitosan (e.g., carboxymethyl chitosan), butyl
20 cyanoacrylate, ethiodol, ethanol, ethanolamine oleate, sotradecol, and combinations thereof. In some cases, an embolic agent including an amnion tissue preparation can be a resorbable (e.g., bioresorbable) amnion coated embolic agents. For example, a resorbable amnion coated embolic agent can be a degradable starch microsphere.

In some cases, embolic agents described elsewhere (see, e.g., Vaidya et al., *Semin. Intervent. Radiol.*, 25:204–215 (2008); EmboMedics; and EmboCept® S) can be obtained,
25 and can be coated with an amnion preparation as described herein.

An embolic agent can be any appropriate size. For example, when an embolic agent is a particle, the particle can be from about 0.5 μm to about 2200 μm (e.g., from about 0.5 μm to about 2000 μm , from about 0.5 μm to about 1750 μm , from about 0.5 μm
30 to about 1500 μm , from about 0.5 μm to about 1250 μm , from about 0.5 μm to about 1000 μm , from about 0.5 μm to about 750 μm , 0.5 μm to about 500 μm , 0.5 μm to about 250 μm , 0.5 μm to about 100 μm , 0.5 μm to about 50 μm , from about 1 μm to about 2200 μm , from about 10 μm to about 2200 μm , from about 25 μm to about 2200 μm , from about 50

5 μm to about 2200 μm , from about 75 μm to about 2200 μm , from about 100 μm to about 2200 μm , from about 250 μm to about 2200 μm , from about 500 μm to about 2200 μm , from about 750 μm to about 2200 μm , from about 1000 μm to about 2200 μm , from about 1500 μm to about 2200 μm , from about 2000 μm to about 2200 μm , from about 1 μm to about 2000 μm , from about 5 μm to about 1500 μm , from about 10 μm to about 1000 μm , from about 25 μm to about 750 μm , from about 50 μm to about 500 μm , from about 100 μm to about 400 μm , from about 200 μm to about 300 μm , from about 1 μm to about 25 μm , from about 25 μm to about 50 μm , from about 50 μm to about 75 μm , or from about 75 μm to about 100 μm) in size (e.g., in diameter or as measured across the longest
 10 dimension).

Amnion coated embolic agents provided herein can include (e.g., be coated with) any appropriate amnion tissue preparation (e.g., human amnion tissue preparation). In cases where an embolic agent is a particle, the particle can be coated with an amnion tissue preparation. For example, embolic agents including an amnion tissue preparation
 15 (e.g., amnion coated embolic agents) can be completely coated with an amnion tissue preparation. In some cases, embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) can be partially coated with an amnion tissue preparation. In some cases, an embolic agent including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can include an amnion tissue preparation (e.g.,
 20 human amnion tissue preparation) as the sole active ingredient. For example, when an embolic agent is an amnion coated embolic agent, an amnion coated embolic agent can include an amnion tissue preparation as the sole active ingredient.

In some cases, an embolic agent including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can include an amnion tissue preparation
 25 (e.g., human amnion tissue preparation) and one or more other therapeutic agents. For example, when an embolic agent is an amnion coated embolic agent, an amnion coated embolic agent can include an amnion tissue preparation and one or more other therapeutic agents. Examples of therapeutic agents include, without limitation, nonsteroidal anti-inflammatory drugs (NSAIDs), cabergoline, selective progesterone receptor modulators,
 30 radiopharmaceuticals, immunosuppressive drugs, angiogenesis inhibitors (e.g., bevacizumab, axitinib, cabozantinib, lenalidomide, regorafenib, vandetanib, ziv-aflibercept, itraconazole, carboxyamidotriazole, TNP-470, CM101, IFN- α , IL-12, platelet factor-4, suramin, SU5416, thrombospondin, VEGFR antagonists, angiostatic steroids +

heparin, cartilage-derived angiogenesis inhibitory factor, matrix metalloproteinase inhibitors, angiostatin, endostatin, 2-methoxyestradiol, tecogalan, tetrathiomolybdate, thalidomide, thrombospondin, prolactin, $\alpha V\beta 3$ inhibitors, linomide, ramucirumab, tasquinimod, ranibizumab, sorafenib, sunitinib, pazopanib, and everolimus), and/or
 5 chemotherapeutic agents (including, but not limited to, alkylating agents (e.g., cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, nitrosoureas, temozolomide), anthracyclines (e.g., daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, and valrubicin), cytoskeletal disruptors (e.g., paclitaxel, docetaxel, abraxane, and taxotere), histone deacetylase inhibitors (e.g., vorinostat and
 10 romidepsin), topoisomerase inhibitors (e.g., irinotecan, topotecan, etoposide, teniposide, and tafluposide), kinase inhibitors (e.g., sorafenib, regorafenib, bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, and vismodegib), nucleotide analogs and precursor analogs (e.g., azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, and tioguanine),
 15 peptide antibiotics (e.g., bleomycin and actinomycin), platinum-based agents (e.g., carboplatin, cisplatin, and oxaliplatin), retinoids (e.g., tretinoin, alitretinoin, and bexarotene), and vinca alkaloids and derivatives (e.g., vinblastine, vincristine, vindesine, and vinorelbine)).

In cases where an embolic agent including an amnion tissue preparation is an
 20 amnion coated embolic agent, an amnion tissue preparation can be coated onto an embolic agent to produce an amnion coated embolic agent provided herein using any appropriate method. For example, in cases where an amnion tissue preparation is a liquid preparation (e.g., solution or suspension), an embolic agent can be dipped into or sprayed with the liquid preparation.

25 In some cases, an amnion tissue preparation can be formulated for transdermal delivery. For example, a composition described herein (e.g., a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can be formulated into a pharmaceutically acceptable composition for administration (e.g., via transdermal delivery) to a mammal (e.g., a mammal having one
 30 or more wounds and/or a skin disorder). For example, a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein can be formulated together with one or more pharmaceutically

acceptable carriers (additives) and/or diluents for transdermal delivery to a human having one or more wounds and/or a skin disorder.

A composition formulated for transdermal delivery as described herein (*e.g.*, a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can be in any appropriate form including, without limitation, solid, liquid, gel, suspension, powder, and granules. For example, a composition can be in any appropriate form for use with transdermal delivery. In some cases, a composition described herein can include one or more delivery vesicles (*e.g.*, non-ionic based surfactant vesicles, and lipid vesicles). In some cases, a composition described herein can be an ionic composition (*e.g.*, cationic or anionic). In some cases, a composition described herein can include one or more chemical penetration enhancers (*e.g.*, alcohols, sulphoxides, azones, pyrrolidones, essential oils, terpenes and terpenoids, fatty acids, water, and/or urea).

A composition formulated for transdermal delivery as described herein (*e.g.*, a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can have any appropriate particle size. A composition can include nanoparticles and/or microparticles. For example, a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein can have a particle size suitable for transdermal delivery. In some cases, a composition can have a particle size ranging from about 0.1 μm to about 100 μm (*e.g.*, from about 0.1 μm to about 75 μm , from about 0.1 μm to about 50 μm , from about 0.1 μm to about 25 μm , from about 0.5 μm to about 100 μm , from about 1 μm to about 100 μm , from about 5 μm to about 100 μm , from about 10 μm to about 100 μm , from about 25 μm to about 100 μm , from about 50 μm to about 100 μm , from about 0.5 μm to about 75 μm , from about 1 μm to about 50 μm , from about 5 μm to about 40 μm , from about 8 μm to about 25 μm , or from about 10 μm to about 20 μm).

In some cases, a composition formulated for transdermal delivery as described herein (*e.g.*, a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can be formulated for a particular transdermal delivery method. For example, when the transdermal delivery method is an electrical transdermal delivery method, the composition can be an ionic composition. Methods of transdermal delivery can be as described elsewhere (see, *e.g.*, Alkilani *et al.*, *Pharmaceutics*, 7:438-470 (2015); Brown *et al.*, *Drug Delivery*, 13:175-

187 (2006); Kalluri *et al.*, *AAPS PharmSciTech*, 12:431-441 (2011); and Kumar *et al.*, *Trop. J. Pharm. Res.*, 6:633-644 (2007)).

In some cases, a composition formulated for transdermal delivery as described herein (e.g., a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can include an amnion tissue preparation (e.g., human amnion tissue preparation) as the sole active ingredient.

In some cases, a composition formulated for transdermal delivery as described herein (e.g., a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can include one or more therapeutic agents, one or more immunosuppressant agents (e.g., corticosteroids (e.g., glucocorticoids), cytostatics, antibodies, calcineurin inhibitors, and interferons), one or more anti-inflammatory agents (e.g., non-steroidal anti-inflammatory drugs, dexamethasone or other type of glucocorticoid steroids), one or more growth factors (e.g., PDGF, EGF, FGF2, or SCF), and/or one or more antimicrobial agents (e.g., antibiotics such as kanamycin, neomycin, streptomycin, or gentamicin, or an antifungal agent).

This document also provides methods for using amnion tissue preparations. In some cases, this document provides methods for using embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein. For example, one or more amnion coated embolic agents (e.g., an effective amount of amnion coated embolic agents) can be administered to a mammal for use in arterial embolization. In some cases, one or more amnion coated embolic agents (e.g., an effective amount of amnion coated embolic agents) can be used to reduce or eliminate blood flow (e.g., blood flow supplying a tumor or hemorrhaging) in a blood vessel of a mammal. For example, a mammal having one or more tumors can be treated by administering one or more amnion coated embolic agents (e.g., an effective amount of amnion coated embolic agents) to reduce or eliminate blood flow supplying a tumor. In some cases, one or more amnion coated embolic agents (e.g., an effective amount of amnion coated embolic agents) can be used to deliver an amnion tissue preparation to a blood vessel (e.g., to promote healing in the blood vessel). Effective amounts of amnion tissue preparations described herein can be determined by a physician, taking into account various factors such as overall health status, body weight, sex, diet, time and route of administration, other medications, and any other relevant clinical factors. As used herein, an “effective amount” or “therapeutically effective amount” of a composition provided herein is the amount that is

sufficient to provide a beneficial effect to the mammal to which the composition or preparations are delivered. In some cases, the effective amount can be the amount effective to reduce and/or eliminate blood flow in a blood vessel of a mammal. For example, the effective amount can be the amount effective to reduce the size of and/or
5 eliminate a tumor in a mammal; to reduce and/or eliminate the number of cells in a tumor; and/or to achieve an improvement or elimination of one or more symptoms of a tumor (e.g., pain, weight loss, loss of appetite, frequent urination, difficulty emptying the bladder, constipation, and jaundice, depending on the type and location of the tumor(s)).

In some cases, one or more embolic agents including an amnion tissue preparation
10 (e.g., amnion coated embolic agents) provided herein can be administered to a mammal as the sole embolic agent used in an arterial embolization.

In some cases, one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can be administered to a mammal together with one or more additional embolic agents (e.g., drug-eluting embolic agents) in
15 an arterial embolization. For example, one or more amnion coated embolic agents can be administered together with one or more embolic agents containing a chemotherapeutic drug (e.g., in a chemoembolization procedure such as transarterial chemoembolization (TACE)). For example, one or more amnion coated embolic agents can be administered together with one or more embolic agents containing a radioactive material (e.g., in a
20 radioembolization procedure such as selective internal radiation therapy (SIRT)).

In some cases, one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can be administered to a mammal in an arterial embolization without inducing an inflammatory response (e.g., an inflammatory response in the blood vessel).

Any appropriate technique can be used to administer one or more embolic agents
25 including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein to a mammal. For example, one or more amnion coated embolic agents provided herein can be administered to a blood vessel in a mammal. In some cases, a catheter can be inserted through a percutaneous puncture in the arm or groin, and one or more amnion
30 coated embolic agents provided herein can be administered to a blood vessel in a mammal via the catheter. In some cases, methods of using amnion coated embolic agents provided herein can include using a guidewire to guide a catheter to a blood vessel. In some cases,

optical imaging (e.g., X-ray, fluoroscopic guidance, and/or radiopaque contrast dye) can be used to guide a catheter to a blood vessel.

Embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can be administered to any appropriate blood vessel. A blood vessel can be an artery, a vein, or a capillary. In some cases, a blood vessel can be a blood vessel supplying a tumor. In some cases, a blood vessel can be a hemorrhagic blood vessel. A blood vessel can be in any appropriate location of the body (e.g., the legs, the neck, the heart, the kidneys, the aorta, the chest, and the abdomen). Examples of blood vessels without limitation, a peripheral artery, a peroneal artery, a plantar artery (e.g., a lateral, medial, or deep plantar artery), a coronary artery, a renal artery, a hepatic artery, and uterine artery. In some cases, one or more amnion coated embolic agents can be administered to a first blood vessel, travel through the vasculature, and form an embolus in a second blood vessel.

In some cases, the methods and materials provided herein can be used to treat a mammal (e.g., a human) having one or more tumors. For example, one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) described herein can be administered to a mammal to reduce and/or eliminate blood flow in a blood vessel supplying a tumor in a mammal. In some cases, the methods provided herein can include reducing blood flow in a blood vessel supplying a tumor in a mammal by about 20% to about 100% (e.g., about 25% to about 95%, about 30% to about 90%, about 50% to about 80%, about 60% to about 75%, about 20% to about 80%, about 20% to about 50%, about 25% to about 50%, about 30% to about 100%, about 40% to about 100%, about 50% to about 100%, or about 75% to about 100%). For example, one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) described herein can be administered to a mammal to reduce and/or eliminate a tumor (e.g., reduce and/or eliminate the size of a tumor and/or reduce and/or eliminate the number of tumor cells in a tumor) in a mammal. In some cases, the methods provided herein can include reducing the size of a tumor in a mammal by about 20% to about 100% (e.g., about 25% to about 95%, about 30% to about 90%, about 50% to about 80%, about 60% to about 75%, about 20% to about 80%, about 20% to about 50%, about 25% to about 50%, about 30% to about 100%, about 40% to about 100%, about 50% to about 100%, or about 75% to about 100%). In some cases, the methods provided herein can

include eliminating (e.g., completely reducing or reducing by 100%) a tumor in a mammal.

In some cases, the methods and materials provided herein can be used to deliver an amnion tissue preparation to a blood vessel. For example, one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) described
5 herein can be administered to a mammal (e.g., a human) to deliver an amnion tissue preparation to a blood vessel. In some cases, the methods provided herein can include delivering, to mammal (e.g., a human), an amnion tissue preparation made with from about 0.01 milligrams (mg) to about 10 grams (g) (e.g., from about 0.01 mg to about 10 g,
10 from about 0.1 mg to about 10 g, from about 1 mg to about 10 g, from about 10 mg to about 10 g, from about 100 mg to about 10 g, from about 1 g to about 10 g, from about 0.01 mg to about 5 g, from about 0.01 mg to about 1 g, from about 0.01 mg to about 100 mg, from about 10 mg to about 5 g, from about 100 mg to about 1 g, or from about 1 g to about 5 g) of amnion tissue preparation to a blood vessel of the mammal being treated.

Any type of mammal can be treated as described herein. Examples of mammals
15 that can be treated with one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein include, without limitation, humans, non-human primates (e.g., monkeys), dogs, cats, horses, cows, pigs, sheep, rabbits, mice, and rats. For example, humans having one or more tumors can be
20 treated with one or more amnion coated embolic agents provided herein.

In some cases, the methods provided herein can include identifying a mammal as having one or more tumors. A mammal can be identified as having a one or more tumors using any appropriate technique. Examples of techniques that can be used to identify a mammal as having a disease and/or disorder associated with tumors, without limitation,
25 imaging techniques, biopsy techniques, and blood tests.

Once identified as having one or more tumors, a mammal can be administered one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein. For example, one or more amnion coated embolic agents provided herein can be administered in an arterial embolization procedure.

30 When treating a mammal (e.g., a human) having one or more tumors, a tumor can be any kind of tumor. A tumor can be benign (not cancerous), pre-malignant (pre-cancerous), or malignant (cancerous).

In some cases, a mammal having one or more tumors can have a disease and/or disorder associated with having tumors. Examples of diseases and/or disorders associated with having tumors include, without limitation, kidney lesions, liver lesions, cancers (e.g., liver cancers such as hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and sarcoma; kidney cancers such as renal cell carcinoma (RCC); neuroendocrine tumors; and ocular melanoma), uterine fibroids, benign prostatic hyperplasias, arteriovenous fistulas (AVFs), and arteriovenous malformations (AVMs). In some cases, one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can be used to treat a mammal having a benign tumor. For example, a human having uterine fibroids can be treated using an amnion coated embolic agent provided herein in an arterial embolization procedure described herein. In some cases, one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can be used to treat a mammal having a cancer. For example, a human having HCC can be treated using an amnion coated embolic agent provided herein in an arterial embolization procedure described herein.

In some cases, the methods and materials provided herein also can be used to treat a mammal (e.g., a human) having excess and/or uncontrolled blood flow (e.g., hemorrhaging) in a blood vessel. For example, one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) described herein can be administered to a mammal (e.g., a human) to reduce and/or eliminate blood flow in a blood vessel. In some cases, the methods provided herein can include identifying a mammal as having excess and/or uncontrolled blood flow (e.g., hemorrhaging) in a blood vessel. A mammal can be identified as having excess and/or uncontrolled blood flow in a blood vessel using any appropriate technique (e.g., angiography (e.g., digital subtraction angiography (DSA) and coronary angiography), ultrasound (e.g., Doppler ultrasound and intravascular ultrasound), and imaging techniques). A mammal having excess and/or uncontrolled blood flow in a blood vessel can have a disease and/or disorder associated with hemorrhaging (e.g., recurrent coughing up of blood, aneurysm (e.g., cerebral aneurysm), internal bleeding (e.g., gastrointestinal bleeding), nosebleeds, varicocele, post-partum bleeding, surgical hemorrhage, and traumatic hemorrhage (e.g., splenic rupture or pelvic fracture)).

Methods for using one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) provided herein can be used as a

combination therapy with one or more additional agents/therapies used to treat one or more tumors. For example, a combination therapy used to treat a tumor can include administering to the mammal (e.g., a human) one or more amnion coated embolic agents provided herein and one or more chemotherapeutic agents (including, but not limited to, 5 alkylating agents (e.g., cyclophosphamide, mechlorethamine, chlorambucil, melphalan, dacarbazine, nitrosoureas, temozolomide), anthracyclines (e.g., daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, and valrubicin), cytoskeletal disruptors (e.g., paclitaxel, docetaxel, abraxane, and taxotere), histone deacetylase inhibitors (e.g., vorinostat and romidepsin), topoisomerase inhibitors (e.g., irinotecan, topotecan, 10 etoposide, teniposide, and tafluposide), kinase inhibitors (e.g., sorafenib, regorafenib, bortezomib, erlotinib, gefitinib, imatinib, vemurafenib, and vismodegib), nucleotide analogs and precursor analogs (e.g., azacitidine, azathioprine, capecitabine, cytarabine, doxifluridine, fluorouracil, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, and tioguanine), peptide antibiotics (e.g., bleomycin and actinomycin), platinum-based agents 15 (e.g., carboplatin, cisplatin, and oxaliplatin), retinoids (e.g., tretinoin, alitretinoin, and bexarotene), vinca alkaloids and derivatives (e.g., vinblastine, vincristine, vindesine, and vinorelbine)). For example, a combination therapy used to treat a tumor can include administering to the mammal (e.g., a human) one or more amnion coated embolic agents provided herein and subjecting the mammal to one or more tumor therapies (e.g., surgery 20 and radiation). In cases where embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) described herein are used in combination with one or more agents/therapies for treating a tumor, the one or more agents/therapies for treating a tumor can be administered/performed at the same time or independently. For example, arterial embolization with one or more amnion coated embolic agents provided herein can 25 be performed first, and the one or more agents/therapies for treating a tumor can be administered second, or vice versa.

In some cases, the methods provided herein also can include confirming the location of the one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) administered to a mammal (e.g., a human) and/or 30 confirming whether or not the one or more embolic agents including an amnion tissue preparation (e.g., amnion coated embolic agents) administered to a mammal (e.g., a human) have formed an embolus (e.g., an artificial embolus). For example, imaging techniques (e.g., DSA) can be performed to confirm the location of the one or more

amniotic coated embolic agents administered to a mammal and/or to confirm that the one or more amniotic coated embolic agents administered to a mammal have formed an artificial embolus.

In some cases, this document provides methods for using a composition described herein (e.g., a composition formulated for transdermal delivery that includes an amniotic tissue preparation described herein and, optionally, a stem cell preparation described herein). In some cases, a composition formulated for transdermal delivery as described herein can be used for treating wounds (e.g., scars) and/or skin disorders (e.g., psoriasis). For example, one or more wounds and/or skin disorders can be treated by administering (e.g., via transdermal delivery) an effective amount of a composition provided herein (e.g., a composition formulated for transdermal delivery that includes an amniotic tissue preparation and, optionally, a stem cell preparation). In some cases, the methods and materials described herein can be used to enhance wound healing. For example, transdermal delivery of a composition that includes an amniotic tissue preparation described herein and, optionally, a stem cell preparation described herein can be used to reduce the size of a wound. In some cases, the methods and materials described herein can be used to treat a skin disorder. For example, transdermal delivery of a composition that includes an amniotic tissue preparation described herein and, optionally, a stem cell preparation described herein can be used to reduce the severity of a skin disorder and/or to reduce one or more symptoms of a skin disorder.

In some cases, the methods and materials for treating mammals (e.g., humans) having one or more wounds and/or a skin disorder can include identifying the mammal as having one or more wounds and/or a skin disorder. Any appropriate method can be used to identify a mammal as having one or more wounds and/or as having a skin disorder. An example of a method that can be used to identify a mammal as having a wound includes, without limitation, physical examination. Examples of methods that can be used to identify a mammal as having a skin disorder include, without limitation, physical examination, prick tests, laboratory tests, and imaging analyses. Once identified as having one or more wounds and/or a skin disorder, the mammal can be transdermally administered or instructed to transdermally self-administer a composition described herein (e.g., a composition that includes an amniotic tissue preparation and, optionally, a stem cell preparation).

Any type of mammal having one or more wounds and/or a skin disorder can be treated using the methods and materials described herein. Examples of mammals that can be treated with a composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation and, optionally, a stem cell preparation) include, without limitation, primates (*e.g.*, humans and non-human primates such as chimpanzees, baboons, or monkeys), dogs, cats, horses, cows, pigs, sheep, rabbits, mice, rats, guinea pigs, gerbils, hamsters, horses, goats, and mammalian zoo animals (*e.g.*, a lion, a tiger, or a leopard). In some cases, the mammal can be a human. For example, a human having one or more wounds and/or a skin disorder can be treated by administering (*e.g.*, via transdermal delivery) a composition that includes an amnion tissue preparation and, optionally, a stem cell preparation.

Any appropriate type of wound can be treated using the methods and materials described herein. The term “wound” as used herein refers to any skin injury in which damage (*e.g.*, abrasion, incision, laceration, puncture, avulsion, or burn) has occurred to skin. A wound can affect any part of the skin including, without limitation, the epidermis (*e.g.*, the stratum corneum), the dermis, and/or the hypodermis. A wound can be an open wound or a closed wound. A wound can be a chronic (*e.g.*, a slow healing) wound. A wound can be a scar. A wound can be located on any part of the body (*e.g.*, arm, leg, foot, hand, belly, chest, and back).

Any appropriate type of skin disorder can be treated using the methods and materials described herein. The term “skin disorder” as used herein refers to any condition that affects (*e.g.*, directly or indirectly) the function of a dermal tissue. Skin disorders can include, without limitation, eczema, psoriasis, rosacea, seborrheic dermatitis, acne, disorders caused by herpes simplex infection (*e.g.*, cold sores), disorders caused by herpes zoster infection (*e.g.*, shingles), skin cancers (*e.g.*, basal cell carcinoma, squamous cell carcinoma and melanoma), sun damage (*e.g.*, actinic keratosis), and pigmentary disorders (*e.g.*, vitiligo, melasma, and lentigenes).

As described herein, one or more wounds and/or skin disorders can be treated by administering (*e.g.*, via transdermal delivery) an effective amount of a composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation and, optionally, a stem cell preparation described herein). In some cases, effective amounts of compositions described herein can be determined by a physician, taking into account various factors such as overall health status, body weight,

sex, diet, time and route of administration, other medications, and any other relevant clinical factors. As used herein, an “effective amount” or “therapeutically effective amount” of a composition provided herein is the amount that is sufficient to provide a beneficial effect to the mammal to which the composition or preparations are administered. The effective amount can be the amount effective to achieve a more rapid recovery, an improvement in the quality of life, reduced wound size, and/or the reduction or elimination of one or more symptoms associated with a mammal’s wound and/or skin disorder.

A composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can be administered using any appropriate technique. In some cases, an amnion tissue preparation described herein can be administered by transdermal delivery. For example, a composition containing an amnion tissue preparation and, optionally, a stem cell preparation described herein can be administered transdermally into the skin near the site of a wound and/or the skin of a mammal having a skin disorder. Transdermal delivery can be passive (*e.g.*, chemical) or active (*e.g.*, physical).

A composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can be administered transdermally using any appropriate method of transdermal delivery. Methods of transdermal delivery that can be used to administer a composition described herein include, without limitation, electrical delivery (*e.g.*, iontophoresis at about 0.1 mA/cm² to about 1.0 mA/cm² and electroporation at about 50 V to about 500 V), mechanical delivery (*e.g.*, microneedle), ultrasound based delivery (*e.g.*, sonophoresis and phonophoresis at frequencies of about 20 kHz to about 16 MHz), thermal ablation delivery (*e.g.*, laser ablation and radiofrequency ablation at about 100 kHz to about 500 kHz), and injection delivery (*e.g.*, microinjection, liquid injection, or dry injection).

In some cases, transdermal delivery methods can include administration (*e.g.*, topical application) of a composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein).

In some cases, transdermal delivery methods can include using a transdermal delivery device for administration (e.g., topical application) of a composition described herein (e.g., a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein). Examples of transdermal delivery devices include, without limitation, ultrasound devices, iontophoresis devices (e.g., iontophoretic delivery systems such as iontophoresis patches), jet injectors (e.g., liquid injectors and dry (e.g., powder) injectors), and microneedle arrays (e.g., microneedle array patches). In some cases, a transdermal delivery device can include a patch (e.g., an adhesive patch). In some cases, a transdermal delivery device can be a needle-free device. In some cases, a transdermal delivery device can include one or more (e.g., 4 or more, 9 or more, 12 or more, 16 or more, 25 or more, 36 or more, 49 or more, 64 or more, 81 or more, or 100 or more) microneedles. A microneedle can be a dissolving microneedle or a biodegradable microneedle. A microneedle can be a silicon microneedle. A microneedle can be less than about 2000 μm in size (e.g., less than about 1000 μm , less than about 750 μm , less than about 500 μm , less than about 250 μm , less than about 200 μm , less than about 175 μm , less than about 150 μm , less than about 125 μm , or less than about 100 μm in size). For example, a microneedle can have a height from about 25 μm to about 2000 μm (e.g., from about 50 μm to about 2000 μm , from about 100 μm to about 2000 μm , from about 200 μm to about 2000 μm , from about 300 μm to about 2000 μm , from about 400 μm to about 2000 μm , from about 500 μm to about 2000 μm , from about 750 μm to about 2000 μm , from about 1000 μm to about 2000 μm , from about 25 μm to about 1500 μm , from about 25 μm to about 1250 μm , from about 25 μm to about 1000 μm , from about 25 μm to about 7500 μm , from about 25 μm to about 500 μm , or from about 25 μm to about 250 μm). For example, a microneedle can have a base width from about 50 μm to about 250 μm (e.g., from about 50 μm to about 225 μm , from about 50 μm to about 200 μm , from about 50 μm to about 175 μm , from about 50 μm to about 150 μm , from about 50 μm to about 125 μm , from about 50 μm to about 100 μm , from about 50 μm to about 75 μm , from about 75 μm to about 250 μm , from about 100 μm to about 250 μm , from about 125 μm to about 250 μm , from about 150 μm to about 250 μm , from about 200 μm to about 250 μm , from about 75 μm to about 225 μm , or from about 100 μm to about 200 μm). For example, a microneedle can have a tip diameter from about 1 μm to about 25 μm (e.g., from about 1 μm to about 22 μm , from about 1 μm to about 20 μm , from about 1 μm

to about 17 μm , from about 1 μm to about 15 μm , from about 1 μm to about 12 μm , from about 1 μm to about 10 μm , from about 3 μm to about 25 μm , from about 5 μm to about 25 μm , from about 8 μm to about 25 μm , from about 10 μm to about 25 μm , from about 12 μm to about 25 μm , from about 15 μm to about 25 μm , from about 3 μm to about 22 μm , from about 5 μm to about 20 μm , or from about 8 μm to about 15 μm).

Transdermal delivery of a composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can result in local exposure to the composition, systemic exposure to the composition, or a combination thereof.

In some cases, transdermal delivery methods described herein also can include, prior to administration of a composition described herein (*e.g.*, a composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein), preparation of the site of administration (*e.g.*, the skin near a wound and/or the skin of a mammal having a skin disorder). Examples of ways that skin can be prepared for transdermal delivery include, without limitation, cleaning, hair removal (*e.g.*, mechanical hair removal such as shaving, plucking, tweezing, and waxing, or chemical hair removal such as using depilatory creams), and applying one or more penetration enhancers (*e.g.*, alcohols, sulphoxides, azones, pyrrolidones, essential oils, terpenes and terpenoids, fatty acids, water, and/or urea).

The transdermal delivery methods described herein can include delivering to a mammal (*e.g.*, a human) a composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) that is made with from about 0.01 mg to about 10 g (*e.g.*, from about 0.01 mg to about 10 g, from about 0.1 mg to about 10 g, from about 1 mg to about 10 g, from about 10 mg to about 10 g, from about 100 mg to about 10 g, from about 1 g to about 10 g, from about 0.01 mg to about 5 g, from about 0.01 mg to about 1 g, from about 0.01 mg to about 100 mg, from about 10 mg to about 5 g, from about 100 mg to about 1 g, or from about 1 g to about 5 g) of amnion tissue per ml and/or per mg.

In cases where a composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) includes a stem cell preparation, the

methods described herein can include delivering to a mammal (*e.g.*, a human) a stem cell preparation (*e.g.*, a stem cell preparation having viable stem cells) that is made from about 0.1 million to about 3 million (*e.g.*, from about 0.3 million to about 3 million, from about 0.5 million to about 3 million, from about 0.75 million to about 3 million, from about 1 million to about 3 million, from about 1.5 million to about 3 million, from about 0.3 million to about 2.5 million, from about 0.3 million to about 2.0 million, from about 0.3 million to about 1.5 million, from about 0.3 million to about 1.0 million, from about 0.5 million to about 2.5 million, from about 0.75 million to about 2.0 million, from about 0.8 million to about 1.5 million) stem cells.

In some cases, a composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can be administered to a mammal (*e.g.*, by transdermal delivery) only once. In some cases, multiple (*e.g.*, two, three, four, five, six, seven, eight, nine, 10, 11, 12, 13, 14, 15, or 20 or more) administrations can be used. For example, multiple administrations of a composition described herein can be made over the course of several (*e.g.*, two, three, four, five, six, seven, eight, nine, 10, 14, 21, 28, or 31 or more) consecutive days (*e.g.*, one delivery each day for seven days or one delivery every other day for seven days). In some cases, a composition described herein can be administered from about once a week to about once per year (*e.g.*, once every month or once every other month). In some cases, a composition described herein can be administered to a mammal for several months (*e.g.*, one delivery per month for six months, or one delivery per week for two months).

A composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can be administered (*e.g.*, by transdermal delivery) to a mammal at various time points after diagnosis with a wound and/or a skin disorder. For example, a composition containing an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein can be administered by transdermal delivery immediately following diagnosis with a wound and/or a skin disorder. In some cases, a composition containing an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein can be administered to a mammal less than 10 (*e.g.*, 9, 8, 7, 6, 5, 4, 3, 2, or 1) days after diagnosis with a wound and/or a skin disorder.

A composition described herein (*e.g.*, a composition formulated for transdermal delivery that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein) can be administered to a mammal as a combination therapy with another treatment used to treat a wound and/or a skin disorder.

5 For example, a combination therapy can include administering to the mammal (*e.g.*, a human) a composition described herein and one or more additional agents that provide a therapeutic effect to the mammal who has a wound and/or skin disorder. In some cases, the composition and the one or more additional agents can be administered at the same time. In some cases, the composition can be administered first, and the one or more
10 additional agents administered second, or vice versa.

In some cases, the methods described herein can include monitoring one or more wounds and/or a skin disorder in the mammal (*e.g.*, to determine the efficacy of the treatment). Any appropriate method can be used to monitor the wound and/or the skin disorder. For example, a wound can be monitored to determine if the wound is healing.

15 In some cases, wound healing can be defined as reducing the size of the wound by at least 5% (*e.g.*, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 55%, at least 60%, at least 65% or more). For example, a skin disorder can be monitored to determine if the severity of the skin disorder and/or one or more symptoms of the skin disorder are being reduced. In some cases, one or more
20 symptoms of the skin disorder can be eliminated.

In some cases, the methods and materials (*e.g.*, embolic agents including an amnion tissue preparation and compositions formulated for transdermal delivery that include an amnion tissue preparation) described herein can be used to treat other diseases and/or disorders including, but not limited to, lung disease, heart disease, neurological
25 disorders, neurological injuries, muscular disorders, and muscular injuries.

In some cases, materials (*e.g.*, embolic agents including an amnion tissue preparation and compositions formulated for transdermal delivery that include an amnion tissue preparation) described herein can be combined with packaging material and sold as a kit. The packaging material included in a kit typically contains instructions or a label
30 describing how the composition can be administered. For example, when a kit includes one or more embolic agents including an amnion tissue preparation, the kit can include instructions or a label for administering the one or more embolic agents including an amnion tissue preparation via arterial embolization (*e.g.*, administration into a blood

vessel of a mammal such as a mammal having one or more tumors). For example, when a kit includes one or more compositions formulated for transdermal delivery that include an amnion tissue preparation, the kit can include instructions or a label for administering the one or more compositions including an amnion tissue preparation via transdermal
5 delivery (e.g., into the skin near a wound and/or into the skin of a mammal having a skin disorder). A kit also can include a unit dose device. The term “unit dose device” refers to a delivery device (e.g., a transdermal delivery device) that administers a single dose of a composition described herein to a user (e.g., a human). Typically, a unit dose device contains a single container that holds or contains a pharmaceutically acceptable
10 composition that includes an amnion tissue preparation described herein and, optionally, a stem cell preparation described herein.

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

OTHER EMBODIMENTS

15 It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A composition comprising an embolic agent comprising a coating comprising an amnion tissue preparation.
2. The composition of claim 1, wherein said embolic agent is a microparticle.
3. The composition of claim 1, wherein said embolic agent is a microsphere.
4. The composition of any one of claims 1-3, wherein said embolic agent comprises a bio-compatible material.
5. The composition of claim 4, wherein said bio-compatible material is selected from the group consisting of tris-acryl gelatin, polyvinyl alcohol, ethylene vinyl alcohol copolymer, poly(lactic-co-glycolic acid), N-butyl-2 cyanoacrylate, collagen, thrombin, glue, calcium alginate, latex, silicon, starch, cellulose, chitosan, butyl cyanoacrylate, ethiodol, ethanol, ethanolamine oleate, sotradecol, and combinations thereof.
6. The composition of any one of claims 1-5, wherein said embolic agent is resorbable.
7. The composition of any one of claims 1-6, wherein said embolic agent is from about 0.5 μm to about 1200 μm in size.
8. The composition of any one of claims 1-7, wherein said amnion tissue preparation comprises viable cells.
9. The composition of any one of claims 1-7, wherein said amnion tissue preparation lacks viable cells.
10. The composition of any one of claims 1-9, wherein said amnion tissue preparation is a dried amnion tissue preparation.

11. The composition of claim 10, wherein said dried amnion tissue preparation has a water content that is less than about 8 percent.
12. The composition of claim 10 or claim 11, wherein said dried amnion tissue preparation has a particle size ranging from about 0.1 μm to about 25 μm .
13. The composition of any one of claims 1-12, wherein said amnion tissue preparation is the sole active ingredient.
14. The composition of any one of claims 1-12, wherein said embolic agent is further coated with one or more therapeutic agents.
15. The composition of claim 14, wherein said one or more therapeutic agents comprise one or more angiogenesis inhibitors.
16. The composition of claim 14, wherein said one or more therapeutic agents comprise one or more chemotherapeutic agents.
17. The composition of claim 14, wherein said one or more therapeutic agents comprise one or more angiogenesis inhibitors and one or more chemotherapeutic agents.
18. An artificial embolus comprising one or more compositions of any one of claims 1-17.
19. A method for performing arterial embolization, said method comprising:
 - administering one or more compositions into a blood vessel of a mammal, wherein said composition comprises an embolic agent comprising a coating comprising an amnion tissue preparation;
 - wherein said one or more embolic agents form an embolus in said blood vessel;
 - and
 - wherein blood flow in said blood vessel is reduced.

20. A method for treating a tumor in a mammal, said method comprising:
administering one or more compositions into a blood vessel of said mammal,
wherein said composition comprises an embolic agent comprising a coating comprising
an amnion tissue preparation;
wherein said one or more embolic agents form an embolus in said blood vessel;
and
wherein the size of said tumor is reduced.
21. The method of claim 20, wherein said tumor is a benign tumor.
22. The method of claim 21, wherein said benign tumor is a uterine fibroid.
23. The method of claim 21, wherein said benign tumor is a benign prostatic hyperplasia.
24. The method of claim 20, wherein said tumor is a cancerous tumor.
25. The method of claim 24, wherein said cancerous tumor is a liver cancer tumor.
26. The method of claim 25, wherein said liver cancer is a hepatocellular carcinoma, a
cholangiocarcinoma, or a sarcoma.
27. The method of claim 24, wherein said cancerous tumor is a kidney cancer tumor.
28. The method of claim 27, wherein said kidney cancer is a renal cell carcinoma.
29. The method of any one of claims 20-28, wherein said mammal is a human.
30. The method of any one of claims 20-29, wherein said composition does not induce an
inflammatory response in said mammal.

31. A method for healing a wound in a mammal, wherein said method comprises:
transdermally administering a composition comprising an amnion tissue
preparation lacking viable cells to said mammal,
wherein the size of said wound is reduced.
32. The method of claim 31, wherein said mammal is a human.
33. The method of claim 31 or claim 32, wherein said wound is selected from the group
consisting of an abrasion, incision, laceration, puncture, avulsion, and burn.
34. The method of claim 31 or claim 32, wherein said wound is a slow healing wound or
a scar.
35. The method of any one of claims 31-34, wherein the size of said wound is reduced by
at least 5%.
36. The method of any one of claims 31-35, wherein said transdermally administering
comprises iontophoresis.
37. The method of claim 36, wherein said iontophoresis comprises from about 0.1
mA/cm² to about 1.0 mA/cm².
38. The method of any one of claims 31-35, wherein said transdermally administering
comprises microinjection.
39. The method of claim 38, wherein said microinjection comprises using a microneedle
array.
40. The method of any one of claims 31-39, wherein said transdermally administering
comprises a transdermal delivery device.

41. The method of claim 40, wherein said transdermal delivery device is an adhesive patch.
42. The method of any one of claims 31-41, wherein said amnion tissue preparation comprises an amnion tissue preparation prepared from about 1 mg to about 10 g of amnion tissue.
43. The method of any one of claims 31-42, wherein said composition further comprises a stem cell preparation having viable cells, and wherein said stem cell preparation comprises from about 0.3 million to about 3 million stem cells.
44. The method of any one of claims 31-43, wherein said amnion tissue preparation is a human amnion tissue preparation.
45. The method of claim 43, wherein said stem cell preparation is a human mesenchymal stem cell preparation.
46. A method for treating a skin disorder in a mammal, wherein said method comprises:
transdermally administering a composition comprising an amnion tissue preparation lacking viable cells to said mammal,
wherein a symptom of said skin disorder is reduced.
47. The method of claim 46, wherein said mammal is a human.
48. The method of claim 46 or claim 47, wherein said skin disorder is selected from the group consisting of eczema, psoriasis, rosacea, seborrheic dermatitis, acne, cold sores, shingles, basal cell carcinoma, squamous cell carcinoma, melanoma, actinic keratosis, vitiligo, melasma, and lentigenes.
49. The method of claim 48, wherein said skin disorder is psoriasis.
50. The method of any one of claims 46-49, wherein said symptom is eliminated.

51. The method of any one of claims 46-50, wherein said transdermally administering comprises iontophoresis.
52. The method of claim 51, wherein said iontophoresis comprises from about 0.1 mA/cm² to about 1.0 mA/cm².
53. The method of any one of claims 46-50, wherein said transdermally administering comprises microinjection.
54. The method of claim 53, wherein said microinjection comprises using a microneedle array.
55. The method of any one of claims 46-54, wherein said transdermally administering comprises a transdermal delivery device.
56. The method of claim 55, wherein said transdermal delivery device is an adhesive patch.
57. The method of any one of claims 46-56, wherein said amnion tissue preparation comprises an amnion tissue preparation prepared from about 1 mg to about 10 g of amnion tissue.
58. The method of any one of claims 46-57, wherein said composition further comprises a stem cell preparation having viable cells, and wherein said stem cell preparation comprises from about 0.3 million to about 3 million stem cells.
59. The method of any one of claims 46-58, wherein said amnion tissue preparation is a human amnion tissue preparation.
60. The method of claim 58, wherein said stem cell preparation is a human mesenchymal stem cell preparation.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/51651

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 35/12, A61K 35/48, A61K 35/50 (2018.01)
 CPC - A61K 35/12, A61K 35/28, A61K 35/50

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.
X --- A	US 2016/0199537 A1 (MIMEDX GROUP, INC.) 14 July 2016 (14.07.2016) Para [0015]; Para [0017]; Para [0025]; Para [0038]; Para [0043]; Para [0046]; Para [0077]; Para [0094]; Para [0105]; Para [0119]; Para [0122]	46-49 ----- 20-29
X --- Y --- A	US 2016/0184479 A1 (FETTECH, LLC) 30 June 2016 (30.06.2016) Para [0001]; Para [0018]; Para [0026]; Para [0027]; Para [0040]; Para [0059]; Para [0060]; Para [0064]; Para [0080]; Para [0098]; Para [0101];	1-5; 31-34 ----- 19 ----- 20-29
Y	CHEN et al. "Percutaneous Thrombin Injection for Treatment of a Splenic Artery Aneurysm", 2006, Radiology Case Reports, Vol. 1(1): pgs. 13-16 Pg. 13, Col. 1, Para [1]; Pg. 14, Col. 1, Para [3]; Pg. 14, Col. 1, Para [4]; Pg. 14, Col. 2, Para [1];	19
A	US 2013/0238100 A1 (AFCELL MEDICAL) 12 September 2013 (12.09.2013) Entire Document	1-5, 19, 31-34, 46-49
A	US 2012/0171180 A1 (ABRAMSON et al.) 05 July 2012 (05.07.2012) Entire Document	1-5, 19, 31-34, 46-49

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search

16 November 2018

Date of mailing of the international search report

06 DEC 2018

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
 P.O. Box 1450, Alexandria, Virginia 22313-1450
 Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/51651

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☒ Claims Nos.: 6-18, 30, 35-45, 50-60
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.