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(54) **COMPOSITIONS AND METHODS FOR
CARTILAGE REPAIR**

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(57) **ABSTRACT**

Autologous compositions and methods are provided for cartilage repair in patients in need thereof. Some aspects include combinations of platelet-based materials with chondrogenesis inducing agents in the presence or absence of cell-based therapies.

COMPOSITIONS AND METHODS FOR CARTILAGE REPAIR

TECHNICAL FIELD

[0001] The invention generally relates to compositions and methods for cartilage repair in patients in need thereof. More particularly, the invention relates to autologous compositions and methods for inducing chondrogenesis at sites in need of cartilage repair in patients in need thereof.

BACKGROUND

[0002] Mesenchymal stem cells are pluripotent blast or embryonic-like cells located in blood, bone marrow, dermis and periosseum. In general, these cells are capable of renewing themselves over extended periods of time as well as, under various environmental conditions, differentiating into cartilage, bone and other connective tissue. Recently, various investigators have researched the potential for using these cells to repair or regenerate target tissues, e.g., bone, cartilage, etc. In this manner MSCs have been reported to have regenerative capabilities in a number of animal models. See Acosta et al. (2005) *Neurosurg Focus* 19(3):E4; Barry (2003) *Novartis Found Symp.* 249:86-102, 170-4, 239-41; Brisby et al. (2004) *Orthop Clin. North Am.* 35(1):85-89; Buckwalter and Mankin (1998) *Instr Course Lect.* 47:487-504; Caplan (1991) *J Orthop Res.* 9(5):641-650.

[0003] Recently, Centeno et al. (U.S. patent application Ser. No. 11/773,774) described a method for expanding MSC's using a growth channel and autologous platelet lysate. Also described were methods for transplanting certain levels of growth factors (platelet lysate or platelets) with the expanded MSC's to the area in a patient in need of repair. The levels of these growth factors were based on a percentage of platelet lysate needed to optimally expand the cells ex-vivo.

[0004] MSC's can readily differentiate in culture depending on cytokine exposure, environmental conditions (pressure, attachment opportunities, passage treatment, etc . . .), or other chemical exposure. For example, exposure to varying levels of TGF-beta, FGF, and/or PDGF can all have impacts on the final cell phenotype produced in culture. In addition, leaving cells in culture longer also has impacts on differentiation potential. Cells can be cultured for a certain visual morphology, confluence, or density, all of which has an impact on the final cell product produced and its potential for certain types of tissue repair.

[0005] In replacing or repairing tissue with MSC's, one concern is the use of autologous or non-autologous cells. While MSC's have been traditionally considered immune privileged, recent investigations have demonstrated their activation of the natural killer cell system in a foreign host. (Spaggiari, Capobianco et al. 2006) This makes the use of non-autologous cells difficult, as it is anticipated that the host's immune system will attack these foreign cells and potentially decimate the population of transplanted MSCs, thus severely limiting their repair capabilities.

[0006] There is a need in the art for MSC expansion techniques that do not use drugs or growth factors which are not FDA approved and can be effectively used to replace tissue in a patient in need thereof. This is especially true where the tissue in the patient in need of repair is cartilage. Cartilage repair is a major issue in health care which will only continue to increase as the median age in the United States continues to increase.

[0007] There is a need for autologous techniques to yield MSC and non-MSC based cartilage repair techniques.

[0008] The present invention is directed toward overcoming one or more of the problems discussed above.

SUMMARY OF THE EMBODIMENTS

[0009] The present invention provides repair compositions for facilitating repair and/or replacement of cartilage in patients in need thereof. Repair compositions include an effective amount of a platelet-based material in combination with one or more chondrogenesis inducing agents. In some cases the platelet-based material and/or the chondrogenesis inducing agent(s) are autologous.

[0010] Aspects of the platelet-based material include one or more of the following solutions: platelet lysate, platelet rich plasma, platelet rich fibrin, and/or whole cell platelet concentrate.

[0011] Aspects of the chondrogenesis inducing agent include growth factors, cytokines, steroid hormones and nutrients for facilitating cartilage formation in patients in need thereof. One or more agents are combined with the platelet-based material. Chondrogenesis inducing agents can be autologous to the patient.

[0012] Repair compositions of the invention can further include cell-based materials, including: mesenchymal stem cells, chondrocytes, isolated bone marrow nucleated cells, chondrocyte progenitor cells, osteoblasts, embryonic stem cells, or stem cells of other lineages. Cells are typically autologous to the patient, being harvested from the patient prior to cartilage repair and expanded to sufficient numbers for optimal treatment.

[0013] Repair compositions of the invention can also include carrier materials, including: gels, hydrogels, absorbable polymers, and the like. Carriers act as scaffolding for cartilage formation within the site of cartilage repair. Carriers can be added to the site of repair contemporaneously with the repair compositions or be part of the repair composition.

[0014] The present invention provides pharmaceutical compositions for use in therapeutic applications. Pharmaceutical compositions herein are used to treat patients having a site in need of cartilage repair, in some cases the patient has osteoarthritis or other like degenerative disease.

[0015] The present invention provides kits having one or more of the following materials: one or more platelet based material, one or more chondrogenesis inducing agent(s), one or more cell based material and one or more carrier. In some aspects the kit includes the materials necessary to harvest the target material from a patient rather than the material itself, for example the tools and supplies necessary to harvest and prepare a platelet lysate. Kits may include vials, tissue culture flasks, culture medium, and other like laboratory materials necessary for the harvest and isolation of materials necessary to practice the present invention.

[0016] The present invention also provides methods for facilitating cartilage repair or replacement in a patient in need thereof. Methods include harvesting and preparing a platelet-based material, for example a 5% to 40% platelet lysate, from a patient having a cartilage repair site in need of treatment; optionally harvesting and preparing a chondrogenesis inducing agent from the same patient, e.g., isolating IGF-1 from the patient, and/or obtaining and administering a non-autologous chondrogenesis inducing agent (such as dexamethasone, ascorbic acid, etc . . .); optionally harvesting and preparing a cell-based therapy from the same patient, e.g., harvesting and

isolating mesenchymal stem cells from the patient's bone marrow, and/or obtaining and administering a non-autologous cell based material; optionally obtaining a carrier material; administering to the repair site a repair composition of the invention; monitoring and re-administering repair compositions of the invention to patient's that require additional treatment for cartilage repair.

[0017] These and various features and advantages of the invention will be apparent from a reading of the following detailed description and a review of the appended claims.

DETAILED DESCRIPTION

Definitions

[0018] The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

[0019] "About" refers to a $\pm 10\%$ variation from the nominal value. It is to be understood that such variation is always included in any given value provided herein, whether or not it is specifically identified.

[0020] "Chondrogenesis inducing agent" refers to any agent capable of inducing or facilitating cartilage formation above the levels of cartilage formation found in a normal and untreated subject. Chondrogenesis inducing agents include but are not limited to; growth factors, cytokines, hormones, and various essential nutrients. Illustrative growth factors include Transforming Growth Factor-beta (TGF- β), Fibroblast Growth Factors (FGFs), Insulin Like Growth Factors (IGFs), Bone Morphogenic Proteins (BMPs); illustrative cytokines including Cytokine-like 1 (Cyt11); illustrative hormones include Human Growth Hormone (HGH); and Testosterone and illustrative essential nutrients include Ascorbic Acid, pyruvate, and amino acids. A chondrogenesis inducing agent can include one or more of the materials as described above, for example a combination of TGF- β and pyruvate.

[0021] "Mesenchymal stem cells" or "MSCs" refers to multipotent stem cells capable of differentiating into osteoblasts, chondrocytes, myocytes, adipocytes, neuronal cells, pancreatic islet cells, and the like. Additionally, methods and compositions detailing MSCs as described in U.S. Pat. Nos. 5,486,359, 6,387,367 and 5,197,985 are incorporated by reference herein in their entirety. In more detail, mesenchymal stem cells are multipotent stem cells located in the bone marrow, peripheral blood, adipose tissue and other like sources. Source MSCs of the invention can be harvested from the iliac crest of the patient in need (or other source such as the IVD, periosteum, synovial fluid, or the vertebral body or pedicle) of the restorative/replacement therapy (or a suitable donor), such patient is referred to herein as a "patient in need or patient in need thereof" (note that other sources, such as adipose tissue, synovial tissue, and connective tissue have recently been identified and are also considered as MSC sources within the scope of the present invention). In one embodiment, approximately 10-100 cc of bone marrow is harvested and "isolated" using methods described in U.S. Patent Application 60/761,441 to Centeno or through adherence to plastic, as described in U.S. Pat. No. 5,486,359 to Caplan et al. Each of these references is incorporated herein in their entirety for all purposes.

[0022] "Platelet lysate" refers to the combination of natural growth factors contained in platelets that have been released through lyses of the platelets. Lyses can be accomplished through chemical means (i.e., CaCl_2), osmotic means (use of

distilled H_2O), or through freezing/thawing procedures. Platelet lysates of the invention can also be derived from whole blood and can be prepared as described in U.S. Pat. No. 5,198,357, which is incorporated by reference herein.

[0023] "Repair" refers to restoration of some or all of a surface's cartilage to an acceptable operating condition. In some instances this may entail a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, and 100+% increase over the untreated condition in the patient in need of cartilage repair.

[0024] "Whole cell platelet concentrate", "platelet rich plasma", and "platelet rich fibrin" are as generally known in the art. For example, platelet rich plasma or PRP can be obtained through methods as described in Landesberg et al., J Oral Maxillofac Surg 58:297, 2000, which is incorporated by reference in its entirety.

Aspects of the Invention

[0025] Aspects of the present invention provide cartilage repair compositions for facilitating cartilage repair in a patient in need thereof. Embodiments include a therapeutically effective amount of platelet lysate in conjunction with one or more chondrogenesis inducing agents. In some cases the platelet lysate is an autologous platelet lysate. In some cases the chondrogenesis inducing agent is an autologous chondrogenesis inducing agent.

[0026] In one embodiment, a repair composition includes a therapeutically effective amount of one or more of a platelet rich plasma, platelet rich fibrin, or a whole cell platelet concentrate in conjunction with one or more chondrogenesis inducing agents. The platelet rich plasma, platelet rich fibrin and/or whole cell platelet concentrate can be autologous. In some cases the platelet rich plasma, platelet rich fibrin and/or whole cell platelet concentrate can replace the platelet lysate. For purposes of the invention, any one or more of platelet lysate, platelet rich plasma, platelet rich fibrin and/or whole cell platelet concentrate will be referred to as a platelet-based material.

[0027] In another embodiment, the repair composition includes a therapeutically effective amount of a combination of a platelet lysate and two or more of platelet rich plasma, platelet rich fibrin or whole cell platelet concentrate in conjunction with one or more chondrogenesis inducing agent(s). As above, either or both of the platelet lysate and two or more of platelet rich plasma, platelet rich fibrin or whole cell platelet concentrate can be autologous. In some embodiments the chondrogenesis inducing agent(s) is also autologous.

[0028] In still another embodiment, a repair composition of the invention herein includes from about 10,000 to 10,000,000,000 mesenchymal stem cells. In typical cases the mesenchymal stem cells are autologous and prepared per methods described in the definition section above or as described in U.S. patent application Ser. No. 11,773,774 (and U.S. Provisional Patent Application No. 61/014,987), which are incorporated herein by reference. Alternatively, about from 10,000 to 10,000,000,000 chondrocytes can be combined with repair compositions of the invention, chondrocytes can be autologous. Autologous chondrocytes can be isolated and expanded using techniques as described herein for MSCs as well as through a review of the relevant art, e.g., Johnson et al., Tissue Engineering, 2004 10(9-10) 1308-1318, incorporated herein by reference. In other embodiments the mesenchymal stem cells or chondrocytes are non-autologous and purchased from a vendor. In general, any combination of cells

useful for inclusion in the repair compositions herein will be referred to as cell-based materials.

[0029] As such, repair compositions as described herein can include one or more of the following: autologous or non-autologous platelet-based material(s); autologous or non-autologous chondrogenesis inducing agent(s); and autologous or non-autologous cell-based materials(s).

[0030] Other aspects of the present invention provide methods for facilitating cartilage repair in a patient in need thereof.

[0031] Methods include, administering a repair composition (e.g., platelet lysate and chondrogenesis inducing agent) of the invention to a site in a patient in need of such therapy. Methods herein would include preparation of the repair composition as either a autologous composition or non-autologous composition. Where any one component of the repair composition is from a non-autologous source (excluding excipients, solutions, e.g., sterile PBS, and other materials required to administer the repair composition) the entire composition is considered non-autologous.

[0032] In another embodiment, the components that make up a repair composition can be administered sequentially, for example, the platelet lysate (and/or platelet rich plasma, platelet rich fibrin and/or whole cell platelet concentrate) and chondrogenesis inducing agent can be administered in a non-contemporaneous manner, for example within one minute of each other, within ten minutes of each other, within one hour of each other, within one day of each other or within one week of each other. Method embodiments herein include any administration procedure that results in the components of the repair composition being administered to the site in need of repair, as long as the administration is directed at repair of the same site in need of repair in the patient in need of repair.

[0033] In still other embodiments of the present invention, methods can include preparing platelet lysate solutions, platelet rich plasma, platelet rich fibrin and/or whole cell platelet concentrates from the patient in need of treatment. These platelet based materials are then autologous to the patient in need of therapy. Methods for isolating and preparing these materials are described in U.S. patent application Ser. No. 11/773,774 and U.S. Provisional Patent No. 61/014,987, which are incorporated herein by reference for all uses.

[0034] As noted above, in some embodiments herein, mesenchymal stem cells are administered in a therapeutic amount to the site in need of cartilage repair either contemporaneously or non-contemporaneously with the repair compositions of the invention.

Cartilage Repair Compositions

[0035] In more detail, composition embodiments of the invention include cartilage repair compositions having an enhanced capacity for cartilage repair in a patient in need thereof. Cartilage repair composition embodiments in accordance with the invention include various combinations of: platelet lysate solution, platelet rich fibrin, platelet rich plasma, and whole cell platelet concentrate with one or more chondrogenesis inducing agent(s). Chondrogenesis inducing agents include various growth factors, cytokines, hormones and nutrients that have been shown to induce or facilitate cartilage growth in the in vivo or in vitro setting.

[0036] In some embodiments, the platelet lysate solution, platelet rich fibrin, platelet rich plasma and/or whole cell platelet concentrate are autologous to the patient receiving the

repair composition. In other embodiments, the chondrogenesis inducing agent(s) is also autologous to the patient receiving the repair composition.

[0037] Autologous platelet-based materials are harvested and prepared as described in U.S. patent application Ser. No. 11/773,774, incorporated herein by reference for all uses. Autologous chondrogenesis inducing agents are obtained per the target agent, for example, growth factors like BMP-7 and BMP-2 can be purchased from Stryker, Inc and Medtronic, cytokines like entanercept (TNF-alpha inhibitor) can be purchased from Amgen/Wyeth, Inc, and the like.

[0038] In typical embodiments the repair compositions include stem cell or cartilage cell growth enhancing compositions of autologous platelet lysate solution. The platelet lysate solution of the invention is typically from about 5% to about 40% platelet lysate, and more typically between about 5% and 20% platelet lysate. Optimal levels of platelet lysate for any given patient can be determined based on bioavailability and concentrations of growth factors in the patients lysate. Optimal levels can be determined by reference to U.S. patent application Ser. No. 11/773,774, incorporated herein by reference for all purposes.

[0039] Typical chondrogenesis inducing agents herein include growth factors that induce or facilitate cartilage growth. Growth factors include: fibroblast growth factor, insulin like growth factor-1, transforming growth factor-beta, bone morphogenetic protein-2, human growth hormone, PDGF-BB, and the like. (see for example: Cassiede et al., J Bone Miner Res., 1996. 11(9): p. 1264-73; Miyata et al., J Cell Physiol., 2005. 204(3): p. 948-55; Kawamura et al., Exp Hematol., 2005. 33(8): p. 865-72; Zhang et al., J Huazhong Univ Sci Technolog Med Sci., 2004. 24(3): p. 275-8; Toh et al., Growth Factors, 2005. 23(4): p. 313-21; Chrisman, O. D., Clin Orthop Relat Res., 1975 (107): p. 232-8; Denko et al., Semin Arthritis Rheum, 2005. 35(1): p. 24-34, each of which is incorporated by references for all purposes herein). Illustrative amounts of chondrogenesis inducing agents include: 1-100 ng/ml (1-500 nM) dose of corticosteroid, 1-500 ng/ml of TGF-beta, 1-500 nM Ascorbic Acid (1-500 mg/ml), FGF-2 of 1-100 ng/mL, 10-500 ng/mL of IGF-1.

[0040] Other typical chondrogenesis inducing agents herein can include cytokines that induce or facilitate cartilage growth. Illustrative cytokines include: interleukin-1 (IL-1) and Cytokine-like 1 (Cyt11). Typical chondrogenesis inducing agents herein can also include steroid hormones like corticosteroid, human growth hormone, testosterone.

[0041] Note also that typical chondrogenesis inducing agents herein can include various cartilage inducing nutrients, for example: glucosamine, hyaluronic acid, (Zhu et al., Stem Cell 2005, incorporated by reference herein for all purposes), collagen, glycoaminoglycans, amino acid mixtures, sodium pyruvate, ascorbic acid, carbohydrates, and the like. (Cassiede et al.; Miyata et al.; Kawamura et al.; Zhang et al.; Toh et al.; Bosnakovski et al., Biotechnol Bioeng., 2006. 93(6): p. 1152-63; Derfoul et al., Osteoarthritis Cartilage, 2007. 15(6): p. 646-55; Song et al., Cytotherapy, 2004. 6(6): p. 596-601, each of which is incorporated by reference in its entirety for all purposes.). In some embodiments, combinations of one or more types of chondrogenesis inducing agents are combined with the platelet-based solutions of the invention, for example: a growth factor in combination with a cytokine, a growth factor in combination with a nutrient, or other like combinations.

[0042] In one embodiment, an about 5% to 40% platelet lysate solution is combined with one or more chondrogenesis inducing agents. Illustrative chondrogenesis inducing agent combinations include IGF-1 and corticosteroid with or without collagen. Platelet lysate with 50 ng/ml of dexamethasone, platelet lysate with ascorbic acid, dexamethasone, and pyrate, and the like.

[0043] In other repair composition embodiments, mesenchymal stem cells are combined with the platelet-based solutions and chondrogenesis inducing agents of the invention. Mesenchymal stem cells are typically autologous and can be harvested and expanded from the patient in need thereof by the methods described above. In alternative embodiments, chondrocytes are combined with the platelet-based solutions and chondrogenesis inducing agents of the invention. Chondrocytes are typically autologous and can be harvested and expanded from the patient in need thereof. In some embodiments a mix of mesenchymal stem cells and various differentiated forms of mesenchymal stem cells (up to and including chondrocytes) are combined with the platelet-based solutions and chondrogenesis inducing agents. Regardless of the nature of the cells, they can be expanded prior to implantation into the patient in need thereof in accordance with aspects of the present invention.

[0044] In still other repair compositions, a carrier material is added to modify the capacity of the embodiments to remain at the site of injury or the timing of release of the composition into the site of injury. Illustrative carriers include: gels, hydrogels, foams, or like materials. These carriers can be combined with the platelet-based materials and chondrogenesis inducing agents with or without cell additives, e.g., mesenchymal stem cells, chondrocytes, etc of the invention. In some aspects the carriers are incorporated as a scaffolding for cell additives or for endogenous cells (generally mesenchymal stem cells or chondrocytes) at or close to the site of injury.

[0045] As noted previously, repair compositions can be administered to a site in need of repair as a single composition or sequentially, where each component of the composition is added at an appropriate time to maximize repair.

Methods Of Inducing Or Facilitating Cartilage Repair In A Patient In Need Thereof

[0046] Embodiments of the invention include therapeutic methods for restoring cartilage at a site in need of repair in a patient in need thereof. For purposes of the invention a site in need of repair is any site in a mammal, e.g., human, horse, dog, etc., in need of cartilage repair or replacement. An illustrative site is a knee joint in a patient having osteoarthritis.

[0047] In one embodiment, an initial determination is made as to what type and how much repair composition would be effective in treating the site in need of repair. This determination is based on site of repair, age of patient, autologous or non-autologous platelet-based lysate, type and amount of chondrogenesis inducing agent, etc. A determination is also made as to the timing of delivery of the different aspects of the repair composition. For example, chondrogenesis inducing agents can be selected for their capacity for degranulation of platelets at an optimal time after administration to the patient. The correct timing in such case must be determined, especially where the platelet-based composition is administered at a time zero and the chondrogenesis inducing agent, e.g., cytokine, is administered at a time X, X representing the optimal time at which to have administered platelet materials degranulate. Various aspects of this initial determination are

described in PCT application PCT/US2008/087452, Compositions and methods to promote implantation and engraftment of stem cells, which is incorporated by reference herein for all purposes.

[0048] Once the above determinations have been made, methods herein require administration of repair compositions of the invention to the patient in need thereof. Administration to the site in need of repair can be accomplished through a surgical incision, arthroscopically, or percutaneously.

[0049] Administration may be performed one or more times in order to maximize cartilage repair or replacement. Injury site analysis can be performed to ensure that acceptable results have been achieved.

Therapeutic Applications

[0050] Repair compositions of the invention provide optimal cartilage repair and/or replacement conditions/environment to repair a site in a patient in need thereof.

[0051] Repair compositions herein can be formulated as pharmaceutical compositions and administered to a patient in need thereof, typically a mammalian, including a human patient. Repair compositions can be formulated in a variety of forms adapted for the chosen route of administration.

[0052] For administration of the compositions of the invention as an injectable solution (whether it be through a surgical incision or arthroscopically), compositions can be formulated according to techniques well-known in the art, using suitable dispersing or wetting agents, such as sterile oils, including synthetic mono- or di-glycerides and fatty acids, including oleic acid.

[0053] Solutions or suspensions of the repair compositions can be prepared in water, isotonic saline (PBS), and optimally mixed with a nontoxic surfactant. Dispersions may also be prepared in glycerol, liquid polyethylene, glycols, vegetable oils, triacetin and mixtures thereof. Under customary use and storage conditions, the repair compositions herein may contain one or more preservatives to prevent growth of microorganisms.

[0054] "Therapeutic applications" herein refers to use of the compositions and methods of the invention to treat a patient having a site in need of cartilage repair or replacement. In some embodiments, the inventions disclosed herein include therapeutic applications in patients having disease states that limit the inherent ability of the patient to repair or re-grow cells at the repair site. For example, patient's that have osteoarthritis.

[0055] The description of the present invention has been presented for purposes of illustration and description, but is not intended to be exhaustive or limiting of the invention to the form disclosed. The scope of the present invention is limited only by the scope of the following claims. Many modifications and variations will be apparent to those of ordinary skill in the art. The embodiment described and shown in the figures was chosen and described in order to best explain the principles of the invention, the practical application, and to enable others of ordinary skill in the art to understand the invention for various embodiments with various modifications as are suited to the particular use contemplated.

[0056] While the invention has been particularly shown and described with reference to a number of embodiments, it would be understood by those skilled in the art that changes in the form and details may be made to the various embodiments disclosed herein without departing from the spirit and scope of the invention and that the various embodiments disclosed

herein are not intended to act as limitations on the scope of the claims. All references cited herein are incorporated in their entirety by reference.

- [0057] 1. Cassiede, P., et al., Osteochondrogenic potential of marrow mesenchymal progenitor cells exposed to TGF-beta 1 or PDGF-BB as assayed in vivo and in vitro. *J Bone Miner Res*, 1996. 11(9): p. 1264-73.
- [0058] 2. Miyata, T., et al., Platelet-derived growth factor-BB (PDGF-BB) induces differentiation of bone marrow endothelial progenitor cell-derived cell line TR-BME2 into mural cells, and changes the phenotype. *J Cell Physiol*, 2005. 204(3): p. 948-55.
- [0059] 3. Kawamura, K., et al., Adenoviral-mediated transfer of TGF-beta1 but not IGF-1 induces chondrogenic differentiation of human mesenchymal stem cells in pellet cultures. *Exp Hematol*, 2005. 33(8): p. 865-72.
- [0060] 4. Zhang, Y., et al., In vitro chondrogenic phenotype differentiation of bone marrow-derived mesenchymal stem cells. *J Huazhong Univ Sci Technolog Med Sci*, 2004. 24(3): p. 275-8.
- [0061] 5. Toh, W. S., et al., Combined effects of TGFbeta1 and BMP2 in serum-free chondrogenic differentiation of mesenchymal stem cells induced hyaline-like cartilage formation. *Growth Factors*, 2005. 23(4): p. 313-21.
- [0062] 6. Chrisman, O. D., The effect of growth hormone on established cartilage lesions. A presidential address to the Association of Bone and Joint Surgeons, 1974. *Clin Orthop Relat Res*, 1975(107): p. 232-8.
- [0063] 7. Denko, C. W. and C. J. Malesud, Role of the growth hormone/insulin-like growth factor-1 paracrine axis in rheumatic diseases. *Semin Arthritis Rheum*, 2005. 35(1): p. 24-34.
- [0064] 8. Zhu, H., et al., The Role of the Hyaluronan Receptor CD44 in MSC Migration in the
- [0065] Extracellular Matrix. *Stem Cells*, 2005.
- [0066] 9. Bosnakovski, D., et al., Chondrogenic differentiation of bovine bone marrow mesenchymal stem cells (MSCs) in different hydrogels: influence of collagen type II extracellular matrix on MSC chondrogenesis. *Biotechnol Bioeng*, 2006. 93(6): p. 1152-63.
- [0067] 10. Derfoul, A., et al., Glucosamine promotes chondrogenic phenotype in both chondrocytes and mesenchymal stem cells and inhibits MMP-13 expression and matrix degradation. *Osteoarthritis Cartilage*, 2007. 15(6): p. 646-55.
- [0068] 11. Song, L., D. Baksh, and R. S. Tuan, Mesenchymal stem cell-based cartilage tissue engineering: cells, scaffold and biology. *Cytotherapy*, 2004. 6(6): p. 596-601.
- [0069] All references herein are incorporated by reference for all purposes.

1. A composition for facilitating cartilage repair in a patient in need thereof comprising a therapeutically effective amount of an autologous platelet lysate and one or more chondrogenesis inducing agents.

2. The composition of claim 1 wherein the platelet lysate is from about 5% to about 40% platelet lysate solution.

3. The composition of claim 1 wherein the chondrogenesis inducing agent is one or more growth factors, one or more cytokines, one or more hormones, or one or more essential nutrients.

4. The composition of claim 3 wherein the chondrogenesis inducing agent is a hormone and wherein the hormone is corticosteroid.

5. The composition of claim 3 wherein the chondrogenesis inducing agent is a growth factor and wherein the growth factor is transforming growth factor β , fibroblast growth factor or a bone morphogenetic protein.

6. The composition of claim 3 wherein the chondrogenesis inducing agent is a cytokine and wherein the cytokine is IL-1.

7. The composition of claim 3 wherein the chondrogenesis inducing agent is an essential nutrient and wherein the essential nutrient is ascorbic acid, collagen, amino acids, peptides, sodium pyruvate, glucose, glutamine, ribonucleosides, carbohydrates, essential oils or deoxyribonucleosides.

8. The composition of claim 1 further comprising platelet rich plasma, platelet rich fibrin, whole cell platelets or a mixture thereof.

9. The composition of claim 1 further comprising a gel, hydrogel, foam, or other carrier material.

10. A method for facilitating cartilage repair in a patient in need thereof comprising:

obtaining platelets from the patient;

preparing a 5% to 40% platelet lysate solution from the platelets;

obtaining one or more chondrogenesis inducing agents; and

administering the 5% to 40% platelet lysate solution and chondrogenesis inducing agent to a site in the patient in need of cartilage repair;

wherein the combined administration of the 5 to 40% platelet lysate solution and chondrogenesis inducing agent facilitates cartilage repair at the site in the patient in need of repair.

11. The method of claim 10 wherein the chondrogenesis inducing agent is one or more growth factors, one or more cytokines, one or more hormones, or one or more essential nutrients.

12. The method of claim 10 further comprising administering a platelet rich plasma, platelet rich fibrin, whole cell platelet or a mixtures thereof to the patient in need thereof wherein the administration is at the site in the patient in need of repair.

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