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Recent Patents Pertaining to Immune Modulation and Musculoskeletal Regeneration with Wharton's Jelly Cells

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Abstract

Umbilical cord mesenchymal stromal cells (UCMSCs) are isolated from Wharton's jelly in the umbilical cord at birth, and offer advantages over adult mesenchymal stromal cells (MSCs) such as highly efficient isolation, faster proliferation *in vitro*, a broader differentiation potential, and non-invasive harvesting procedure. Their expansion and differentiation potential renders them a promising cell source for tissue engineering and clinical applications. This review discusses recent updates on the differentiation strategies for musculoskeletal tissue engineering including cartilage, bone, and muscle. In addition to tissue engineering applications, UCMSCs can be utilized to support hematopoiesis and modulate immune response. We review the patents relevant to the application of MSCs including UCMSCs in hematopoiesis and immune modulation. Finally, the current hurdles in the clinical translation of UCMSCs are discussed. During clinical translation, it is critical to develop large-scale manufacturing of UCMSCs as well as the composition of expansion and differentiation media. Four clinical trials to date have examined the safety and efficacy of UCMSCs. Once public banking of UCMSCs is available to supply matched allogeneic units and once UCMSC manufacturing is standardized, we anticipate that UCMSCs will be more widely used in clinical trials.

Keywords

Clinical study; commercialization; immune modulation; mesenchymal stromal cell; umbilical cord; Wharton's jelly

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CONFLICT OF INTEREST

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1. INTRODUCTION

Mesenchymal stromal cells (MSCs) are a heterogeneous population of multipotent cells that have been isolated from various tissues such as bone marrow, skeletal muscle, perivascular tissue, dental pulp, bone, placenta, amnion, umbilical cord blood, Wharton's jelly, and adipose tissue [1]. The focus of this review is on the Wharton's jelly in the umbilical cord which harbors umbilical cord mesenchymal stromal cells (UCMSCs). UCMSCs offer advantages over adult-derived MSCs such as highly efficient isolation, faster proliferation *in vitro*, a broader differentiation potential, and non-invasive harvesting procedure [2]. Compared to undifferentiated embryonic stem cells (ESCs), undifferentiated UCMSCs do not appear to develop teratomas after transplantation [3]. The investigation of UCMSCs for use in regenerative medicine began in the last decade and is undergoing a rapid expansion. Two patents reported the chondrogenic differentiation of UCMSCs [4, 5] for tissue engineering products at the end of the 1990s. The enthusiasm for UCMSCs increased after Mitchell *et al.* [6] published their article regarding the neuronal differentiation of UCMSCs in *Stem Cells*. UCMSCs may differentiate along several cell lineages in all three germ layers including chondrogenic, osteogenic, adipogenic, cardiomyogenic, pancreatic, neurogenic, and hepatogenic [2]. The expansion potential and multipotency of UCMSCs renders them an attractive MSC source for tissue engineering applications.

In addition to the application of MSCs in tissue engineering, MSCs have been shown to provide stromal support for hematopoiesis and have immunomodulatory capability [7]. MSCs have low immunogenicity, which can be partially attributed to the low expression of major histocompatibility complex (MHC) molecules [8]. MSCs have the capacity to treat immune disorders such as graft-versus-host diseases (GVHD) and autoimmune diseases [9]. In the cell therapy industry, there are many patents and clinical studies that use MSCs as immunomodulatory agents. The vast majority of them utilize bone marrow MSCs (BM-MSCs), while UCMSCs may be an alternative due to their similar immune properties with BM-MSCs. For example, of the 274 clinical trials worldwide found on the Clinicaltrials.gov website (search Nov. 2012), 34% use MSCs for treating immune disorders.

There are several reviews regarding UCMSCs including their biological properties [10, 11], musculoskeletal regeneration [2], skin regeneration [12], immune properties [13, 14], future clinical applications [15], and a patent review on cell isolation and their application on cell therapy [16]. In this review, we first discuss recent updates on differentiating UCMSCs along musculoskeletal lineages including chondrogenic, osteogenic, and myogenic lineages as well as relevant patents. Subsequently, we review the application of MSCs, including UCMSCs, in hematopoiesis and immune modulation. Given that the number of patents related to UCMSCs is much smaller than MSCs in general, the context is provided for the intellectual property (IP) and clinical trial landscape for MSCs for the purpose of looking down the road at where UCMSCs may continue to expand in their own IP landscape.

2. MUSCULOSKELETAL REGENERATION WITH UCMSCS

The differentiation ability of MSCs has a significant impact on the quality of tissue engineering products and their therapeutic performance *in vivo*. The majority of UCMSC

patents describe isolation techniques of MSC-like cells from various anatomical compartments within the umbilical cord, and subsequently demonstrate the differentiation ability and other MSC-like characteristics such as morphology and expansion using established protocols. These differentiation protocols commonly result in slower and less complete chondrogenic and osteogenic differentiation of UCMSCs relative to BM-MSCs as indicated by decreased deposition of chondrogenic or osteogenic signature molecules (2). In this section, we first focus on the methods to improve chondrogenic, osteogenic, and myogenic differentiation of UCMSCs in the literature, and then review recent patents that use UCMSCs as a cell source for tissue engineering.

2.1. Musculoskeletal Differentiation of UCMSCs

UCMSCs differentiate along a chondrogenic lineage upon the stimulation of transforming growth factors (TGF-βs); although TGF-βs alone lead to the formation of fibrocartilage with the coexistence of types I and II collagen [17]. Two different two-stage differentiation strategies have been described that led to enhanced chondrogenesis of UCMSCs when they were embedded in three-dimensional (3D) scaffolds. In one of the differentiation protocols [18], UCMSCs were first exposed to a medium containing insulin-transferrin-selenium (ITS) and basic fibroblast growth factor (bFGF), and then differentiated in chondrogenic media containing TGF-β3 in polycaprolactone/collagen nanoscaffolds. The pre-treatment of UCMSCs using bFGF increased glycosaminoglycan production and upregulated chondrogenic gene expression including type II collagen and SRY (sex determining region Y)-box 9. In the second protocol, the sequential application of TGF-β3 and insulin growth factor-1 to UCMSCs improved chondrogenesis by upregulation of type II collagen gene and protein expression [19].

Traditional osteogenic induction of MSCs including dexamethasone, dihydroxyvitamin D3, and bone morphogenetic protein 2 (BMP-2) induces osteogenic differentiation of UCMSCs [20, 21]. There are many protocols to isolate different populations of UCMSCs from umbilical cord tissues [16], and the isolated populations may have various osteogenic abilities. The population obtained from Wharton's jelly by enzyme digestion or explant culture showed matrix mineralization that was inferior to adult MSCs [22, 23]. A population of umbilical cord perivascular cells (UCPVCs) may be isolated by enzymatically digesting the perivascular area of umbilical cord vessels, and appeared to possess a striking osteogenic ability as evidenced by more bone nodules *in vitro* than BM-MSCs following osteogenic differentiation [24]. One patent [25] described the isolation of UCPVCs. This population was obtained by two-stage adhesion of UCPVCs to plastic surfaces, whereby the cell solution after collagenase digestion was first transferred to cell culture flasks for plastic adhesion, and the supernatant after cell adhesion was then transferred to a new cell culture flask for prolonged adhesion. The cells obtained from the second adhesion were able to rapidly form bone nodules and fat cells, although the timeline for each adhesion was not provided in the patent.

Myogenic differentiation and fusion of UCMSCs may be induced by various techniques including 5-azacytidine [26], gene transfection with MyoD transcription factor [27], or coculture with C2C12 myoblasts [28]. In a dystrophic murine model, human UCMSCs were

able to engraft into damaged muscle. These engrafted cells exhibited a low level of myogenic genes *in vivo*, including the lower expression of dysferlin and human-dystrophin genes than adipose MSCs (ADMSCs) [29]. Grabowska *et al.* [28] reported enhanced muscle regeneration by pre-treatment of UCMSCs with stromal cell-derived factor-1 before cell transplantation. Further examination revealed that the improved regeneration was not due to increased incorporation of UCMSCs into new muscle fibers, but possibly instead to trophic effects of UCMSCs that could help host stem cell homing to damaged muscle sites. Recent reports have indicated a cardiomyogenic potential with fetal MSCs [30, 31], and suggested that UCMSCs may have enhanced cardiomyogenic potential compared to fetal and adult BM-MSCs [32].

2.2. Patents on Tissue Engineering Compositions for Musculoskeletal Regeneration

UCMSCs could be cultured in 3D scaffolds to form specific tissue analogs for implantation in a tissue engineering approach. The formed tissue analogs could also be decellularized to produce therapeutic extracellular matrices. Five patents describe tissue engineering compositions using UCMSCs for cartilage and bone regeneration [4, 5, 25, 33, 34].

Cartilage regeneration is the first application of UCMSCs in the field of tissue engineering and regenerative medicine [4]. In the patent by Purchio *et al.* UCMSCs were named as “pre-chondrocytes”, which were induced toward the chondrocyte phenotype by traditional chondrogenic stimulation. The “pre-chondrocytes” were seeded into a 3D framework and cultured to form cartilage-like tissues containing type II collagen [4, 5]. In another patent [33], an interesting subcutaneous model was used to evaluate *in vivo* chondrogenesis of UCMSCs. UCMSCs were seeded into poly(epsilon-caprolactone)/poly(glycolic acid) scaffolds loaded with TGF-β3 and/or growth differentiation factor 5 (GDF-5). This composition was an excellent example of the integration of cells, scaffolds, and growth factors in a single construct to promote tissue regeneration. The scaffolds were then inserted into cartilage defects that were created in bovine cartilage explants. The explants were finally implanted subcutaneously in mice. It was shown that cartilage regeneration was less pronounced for UCMSCs than for bone marrow and placenta-derived cells, which is consistent with the findings in the literature [17].

Two patents described the fabrication of bone-like tissues *in vitro* by differentiating UCPVCs using osteoconductive scaffolds and co-culture of UCPVCs with hematopoietic stem cell (HSC) expansion [25, 34]. Davies *et al.* [25] cultured UCPVCs in calcium phosphate/poly(lactic-co-glycolic acid) scaffolds for 14 days. At the end of the culture period, the scaffolds were fully covered by cells and bone matrix indicating the potential of UCPVCs for bone regeneration. In another application, Vitelli *et al.* [34] described a process to co-culture UCPVCs and HSCs for growing human tissues *in vitro*, including bone. UCPVCs and HSCs were co-cultured for 12 days at a ratio of 9:1 in a bioreactor containing microcarriers, though the inventors did not report the results regarding tissue formation. The presence of HSCs accelerated osteogenic differentiation of BM-MSCs [35], though the trophic effect of HSCs on UCMSCs differentiation awaits examination.

3. IMMUNE MODULATION OF MSCS

3.1. MSCs have Stromal Support and Immune Modulation Properties

MSCs have utility in tissue engineering and regenerative medicine because they can differentiate into bone, fat, or cartilage [36]; they can also differentiate to cardiomyocytes [37-40] and/or fuse with skeletal muscle [41]. MSCs have additional functions that can be used for regenerative medicine or cellular therapy purposes called stromal support and immune modulation. MSCs reside in the hematopoietic niche and aid in hematopoietic stem/progenitor cell expansion [42, 43]. This function can be demonstrated both *ex vivo* by using MSCs as a feeder layer for expansion of HSCs, or *in vivo* when MSCs are co-grafted with HSCs [44-50]. Hematopoietic expansion by MSCs is caused by indirect and direct interactions, e.g., via the release of cytokines or growth factors by MSCs into the niche (indirect effect) and by their extracellular matrix impinging upon hematopoietic stem/progenitor cell surface receptors (direct effect).

Similar to the effect of MSCs on HSCs, MSCs have both direct and indirect effects upon the immune system [9, 51-65]. MSCs have low immunogenicity, perhaps due to the low expression of MHC molecules, and MSCs suppress the proliferation of activated T cells. Direct and indirect effects most likely mediate these two effects, respectively. The low immunogenicity of MSCs means that they are not attacked by the immune system following allogeneic transplantation into naïve hosts [66]. In contrast, multiple injections of allogeneic MSCs can and do induce an immune response (antibody titer) and MSCs are subsequently scavenged by the immune system (rejected) [66]. In addition, MSCs injected into an existing inflammatory environment may rapidly induce a host immune response and are cleared by the immune system [66]. These cells are cleared because they respond to IFN-γ and probably other inflammatory cytokines found in this environment by upregulation of MHC class I as well as induction of MHC class II on the surface of MSCs [66]. Activation of MSCs by cytokines such as IFN-γ is a double-edged sword. On one hand, IFN-γ activation increases the possibility of immune surveillance via upregulation/induction of MHC molecules (as indicated from PS Cho *et al.*'s work cited above); on the other hand, IFN-γ activation enhances MSCs' immune modulatory effects for treating graft versus host disease (GVHD) [67].

One aspect of immune modulation by MSCs is the suppression of T cell proliferation. This immunomodulation can be observed using a mixed lymphocyte reaction *in vitro*, or observed by MSCs' impact on immune disorders such as GVHD *in vivo* [9, 52, 58-61, 68-73]. Similar to the effect MSCs have on hematopoietic expansion, the suppressive effect of MSCs on the expansion of activated T cells is mediated by both indirect means, such as by chemokines/cytokines like indoleamine 2,3 dioxygenase (IDO), nitric oxide (NO) or prostaglandin E2 (PGE2), and by direct means via MSC - T cell interaction via Toll-like receptors [74-76]. As mentioned above, MSCs' immune modulation/suppression has been useful in treating diseases in which the immune system plays an important role. MSCs are being tested in clinical trials as a cellular therapy for immune-related disorders such as multiple sclerosis, arthritis, myocardial infarction, stroke, neurodegenerative disease, acute spinal cord injury, as well as for iatrogenic immune diseases such as graft versus host

disease (42 clinical trials found on CLINICALTRIALS.GOV using the search term "mesenchymal stromal cells" 25 Sept. 2012; indications include arthritis, Crohn's, myocardial ischemia, graft versus host disease, osteogenesis imperfect, emphysema, multiple sclerosis, diabetic foot ulcers, *ex vivo* expansion of cord blood, spinal cord injury, Parkinson's disease, stroke, liver regeneration, critical limb ischemia, recto-vaginal fistula, and graft augmentation). As discussed below, many of the patents have leveraged the utility of MSCs for stromal support function to enable engraftment and hematopoietic recovery and to treat various inflammatory or immunological disorders.

3.2. Identification of Relevant Patents

Relevant patents (and patent applications) were found using a two round strategy. In the first round, patents were identified by searching the US Patent office website using Quick Search or the International patents using LexisNexis. The search terms were as follows: "mesenchymal stromal cells" AND ("immune" OR "graft"). The search results were stored in a Microsoft Word file. In the second round, the patent abstracts were scanned for relevance. Due to the number of patents (> 268 patents), volume (> 1000 pages scanned), and the writing style (patents use broad statements), relevant patents may have been missed in the search. The results of the search are shown in Tables **1**-**3**. We found issued US patents and did not find issued International patents. We found a number of pending applications in both the US and International patent office. We also found what appear to be repetitive patent applications (patents with the same inventors and title, and a different application number). All relevant patents were included in Tables **1**-**3** and stratified by stromal support function or immune modulation.

3.3. Patents Related to MSCs Providing Stromal Support

The breadth, subtlety, and nuance of patent language make it difficult to provide a fine grain review of the IP landscape, so we provide a 10,000 meter overview below. Twelve issued US patents described the use of MSCs for providing stromal support or enabling hematopoietic engraftment (see Table **1**). Eleven of these patents described the use of bone marrow-derived MSCs and one patent utilized placenta-derived MSCs (7700090 [77]). Several patents described leveraging indirect means of MSC stromal support via diffusible factors/cytokines, and others leveraged indirect and direct effects by permitting direct contact of MSCs with hematopoietic stem/progenitor cells. Thus, the patents described methods of using MSCs *ex vivo* as an MSC feeder layer during *ex vivo* hematopoietic cell expansion (such as US5437994 [78], US5605822 [79], US5879940 [80], US7534609 [81]) or in a device that permits MSCs to condition the medium prior to delivery to the hematopoietic cell culture (US7678573 [82], US7700090 [77]). Some patents described the use of bioreactors for expansion of hematopoietic cells prior to grafting. Other patents described the co-infusion of MSCs with the hematopoietic cells (US5733542 [83], US6010696 [84]) to enable or enhance engraftment. In addition, patents described the use of MSCs for remediation of radiation injury, which would injure the hematopoietic niche including the stroma compartment.

3.4. Patents Related to MSCs Providing Immune Modulation

Seventeen issued US patents described the use of MSCs for immune modulation, including inflammatory disease or immune suppression, treatment of immune disorders, or enabling engraftment (see Table **1**-**3**). Thirteen of these patents involved the use of bone marrow-derived MSCs; the other patents described the use of MSCs obtained from placental (US7682803 [85], US8216566 [86]) and adipose tissue (US8241621 [87]). One patent (US7799324 [88]) described the use of ESCs for immune modulation. In addition to issued patents, twelve US patent applications described the use of MSCs for immune modulation.

4. COMMERCIALIZATION AND CLINICAL TRIALS

Osiris, a Baltimore, Maryland-based biotechnology company, has the largest number of issued patents in this space (US6010696 [84], US6281012 [89], US6328960 [90], US6355239 [91], US6368636 [92], US6685936 [93], US6797269 [94], US6875430 [90], US7029666 [95]). Osiris used its scientific expertise and IP position to make an MSC product called Prochymal. Prochymal is in clinical testing (14 clinical trials listed at CLINICALTRIAL.GOV using the search term “Prochymal” on 23 Sept 2012). A second bio-technology firm, Pluristem, has developed an MSC product they call PLX. PLX is in clinical trials (4 clinical trials listed at CLINICALTRIAL.GOV using the search term “Pluristem” on 24 Sept 2012). A third biotechnology company, Celgene, has developed an MSC product using placenta- derived MSCs called PDA001. PDA001 is in clinical testing (5 clinical trials listed at CLINICALTRIAL.GOV using the search term “Celgene” AND “placenta” on 24 Sept. 2012). A fourth biotechnology company, Athersys, has developed an MSC derivative product using the multipotent adult progenitor cells (MAPC) called MultiStem. MultiStem is in clinical testing (5 clinical trials listed at CLINICALTRIAL.GOV using the search term “Athersys” on 25 Sept 2012).

5. CURRENT & FUTURE DEVELOPMENTS

MSCs show great promise in the field of tissue engineering, hematopoietic stem/progenitor cell support and immune modulation as shown in Fig. (**1**). In the field, there are a considerable number of patents, and many of them are being translated to clinical trials, product development and commercialization as shown in Fig. (**2**). In contrast, UCMSCs have not been employed in clinical studies in the USA. While presenting many merits over adult MSCs, such as the abundant supply of umbilical cords, faster proliferation, and non-invasive harvesting procedure, etc., as listed in the Introduction, the lack of public UCMSC banking is a factor that is limiting their clinical translation in the USA. Umbilical cords are also an important source for endothelial cells, hyaluronic acid and umbilical cord blood, thus offering the possibility to cryopreserve these cells at birth. UCMSCs are able to differentiate along bone, cartilage and fat lineages, though UCMSCs may show slower differentiation with decreased deposition of osteogenic or chondrogenic signature molecules relative to BM-MSCs upon the stimulation of traditional differentiation factors (as discussed above). As we reviewed above, effective *in vitro* differentiation of UCMSCs may require multiple steps and multiple signals. It is of paramount importance to identify the suitable differentiation factors to UCMSCs and optimize their concentration and the timeline of applying multiple factors. Moreover, there is an urgent need for standard operation

procedures to manufacture undifferentiated UCMSCs and their differentiated progeny under Good Manufacturing Practice (GMP) conditions for clinical translation.

Toward early phase clinical application of MSCs, two major concerns are safety (Phase I testing) and efficacy (Phase II testing). Although MSCs have low immunogenicity, some studies show that MSCs are not intrinsically immunoprivileged, indicative of a risk of rejection of allogeneic MSCs following transplantation. For example, when allogeneic BM-MSCs were subcutaneously implanted in an *in vivo* rat osteogenic model, none of the grafts survived unless the FK506 immunosuppressant was given [96]. Multiple injections of undifferentiated allogeneic UCMSCs elicited an immune response, illustrating the potential importance of tissue matching in allogeneic application of MSCs [97]. Moreover, the immune properties of differentiated cells from MSCs have been scarcely explored in the literature. *In vitro* chondrogenic differentiation of UCMSCs resulted in a slight increase in MHC-II and costimulator molecule expression [98], while the implantation of *in vitro* chondrogenically differentiated human UCMSCs did not lead to immune rejection in both rabbit and rat models. In addition, *in vitro* osteogenic differentiation of BM-MSCs and ADMSCs did not affect the expression of MHC-II [99]. Finally, the usage of a xenogeneic component (e.g., fetal bovine serum) during *in vitro* expansion of MSCs has also posed safety risks for transmitting diseases across species and for eliciting immune rejection. Recent efforts have focused on developing serum-free media, or using human serum and platelet lysate or platelet-rich plasma as substitutes for fetal bovine serum. Finally, the efficacy of MSCs has been shown in many pre-clinical studies, while an urgent need is to demonstrate clinical efficacy of MSCs using well-designed clinical.

In conclusion, UCMSCs hold extraordinary potential for musculoskeletal regeneration, to provide for stromal support and immune modulation. While many hurdles exist in the clinical translation of UCMSCs, an immediate priority is to develop scalable processes for manufacturing UCMSCs as well as the composition of expansion and differentiation media. Moreover, the safety and efficacy of UCMSCs remains to be examined in clinical trials, relative to other MSCs, which have an established precedent that we have outlined above that can be built upon with UCMSCs.

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REFERENCES

1. Shi Y, Su J, Roberts AI, Shou P, Rabson AB, Ren G. How mesenchymal stem cells interact with tissue immune responses. Trends Immunol. 2012; 33(3):136–43. [PubMed: 22227317]
2. Wang L, Ott L, Seshareddy K, Weiss ML, Detamore MS. Musculoskeletal tissue engineering with human umbilical cord mesenchymal stromal cells. Regen Med. 2011; 6(1):95–109. [PubMed: 21175290]
3. Fong CY, Richards M, Manasi N, Biswas A, Bongso A. Comparative growth behaviour and characterization of stem cells from human Wharton's jelly. Reprod Biomed. 2007; 15(6):708–18.
4. Purchio, AF.; Naughton, BA.; Roman, JS. Production of cartilage tissue using cells isolated from Wharton's jelly.. 1999. US5919702

5. Naughton, GK.; Naughton, BA. Three dimensional stromal tissue cultures.. 1999. US5962325
6. Mitchell KE, Weiss ML, Mitchell BM, Martin P, Davis D, Morales L, et al. Matrix cells from Wharton's jelly form neurons and glia. Stem Cells. 2003; 21(1):50–60. [PubMed: 12529551]
7. Hao L, Sun H, Wang J, Wang T, Wang M, Zou Z. Mesenchymal stromal cells for cell therapy: Besides supporting hematopoiesis. Int J Hematol. 2012; 95(1):34–46. [PubMed: 22183780]
8. Le Blanc K, Tammik L, Sundberg B, Haynesworth SE, Ringden O. Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scand J Immunol. 2003; 57(1):11–20. [PubMed: 12542793]
9. McGuirk JP, Weiss ML. Promising cellular therapeutics for prevention or management of graft versus host disease (a review). Placenta. 2011; 32(Suppl 4):S304–S10. [PubMed: 21658764]
10. Can A, Karahuseyinoglu S. Concise review: Human umbilical cord stroma with regard to the source of fetus derived stem cells. Stem Cells. 2007; 25(11):2886–95. [PubMed: 17690177]
11. Troyer DL, Weiss ML. Wharton's jelly derived cells are a primitive stromal cell population. Stem Cells. 2008; 26(3):591–9. [PubMed: 18065397]
12. Yang S, Huang S, Feng C, Fu X. Umbilical cord derived mesenchymal stem cells: Strategies, challenges, and potential for cutaneous regeneration. Front Med. 2012; 6(1):41–7. [PubMed: 22460447]
13. McGuirk JP, Weiss ML. Promising cellular therapeutics for prevention or management of graft-versus-host disease (a review). Placenta. 2011; 32(Suppl 4):S304–10. [PubMed: 21658764]
14. La Rocca G, Corrao S, Lo Iacono M, Corsello T, Farina F, Anzalone R. Novel immunomodulatory markers expressed by Human WJ-MSC: An updated review in regenerative and reparative medicine. Open Tissue Eng Regen Med J. 2012; 5:50–8.
15. Taghizadeh RR, Cetrulo KJ, Cetrulo CL. Wharton's Jelly stem cells: Future clinical applications. Placenta. 2011; 32(Suppl 4):S311–5. [PubMed: 21733573]
16. Anzalone R, Farina F, Zummo G, La Rocca G. Recent patents and advances on isolation and cellular therapy applications of mesenchymal stem cells from human umbilical cord Wharton's jelly. RPRM. 2011; 1(3):216–27.
17. Wang L, Tran I, Seshareddy K, Weiss ML, Detamore MS. A comparison of human bone marrow derived mesenchymal stem cells and human umbilical cord-derived mesenchymal stromal cells for cartilage tissue engineering. Tissue Eng Part A. 2009; 15(8):2259–66. [PubMed: 19260778]
18. Fong CY, Subramanian A, Gauthaman K, Venugopal J, Biswas A, Ramakrishna S, et al. Human umbilical cord Wharton's jelly stem cells undergo enhanced chondrogenic differentiation when grown on nanofibrous scaffolds and in a sequential two stage culture medium environment. Stem Cell Rev. 2012; 8(1):195–209. [PubMed: 21671058]
19. Wang L, Detamore MS. Insulin like growth factor-I improves chondrogenesis of predifferentiated human umbilical cord mesenchymal stromal cells. J Orthop Res. 2009; 27(8):1109–15. [PubMed: 19195026]
20. Wang L, Singh M, Bonewald LF, Detamore MS. Signalling strategies for osteogenic differentiation of human umbilical cord mesenchymal stromal cells for 3D bone tissue engineering. J Tissue Eng Regen Med. 2009; 3(5):398–404. [PubMed: 19434662]
21. Hou T, Xu J, Wu X, Xie Z, Luo F, Zhang Z, et al. Umbilical cord Wharton's Jelly: A new potential cell source of mesenchymal stromal cells for bone tissue engineering. Tissue Eng Part A. 2009; 15(9):2325–34. [PubMed: 19231937]
22. Majore I, Moretti P, Stahl F, Hass R, Kasper C. Growth and differentiation properties of mesenchymal stromal cell populations derived from whole human umbilical cord. Stem Cell Rev. 2011; 7(1):17–31. [PubMed: 20596801]
23. Toupadakis CA, Wong A, Genetos DC, Cheung WK, Borjesson DL, Ferraro GL, et al. Comparison of the osteogenic potential of equine mesenchymal stem cells from bone marrow, adipose tissue, umbilical cord blood, and umbilical cord tissue. Am J Vet Res. 2010; 71(10):1237–45. [PubMed: 20919913]
24. Baksh D, Yao R, Tuan RS. Comparison of proliferative and multilineage differentiation potential of human mesenchymal stem cells derived from umbilical cord and bone marrow. Stem Cells. 2007; 25(6):1384–92. [PubMed: 17332507]

25. Davies, JE.; Baksh, D.; Sarugaser, R.; Hosseini, M. Lickorish A.D.S. Progenitor cells from Wharton's jelly of human umbilical cord.. 2009. US20090269318
26. Liu J, Zhou H, Weir MD, Xu HH, Chen Q, Trotman CA. Fast degradable microbeads encapsulating human umbilical cord stem cells in alginate for muscle tissue engineering. Tissue Eng Part A. 2012; 18(21-22):2303–14. [PubMed: 22697426]
27. Kocaefe C, Balci D, Hayta BB, Can A. Reprogramming of human umbilical cord stromal mesenchymal stem cells for myogenic differentiation and muscle repair. Stem Cell Rev. 2010; 6(4):512–22. [PubMed: 20665127]
28. Grabowska I, Brzoska E, Gawrysiak A, Streminska W, Moraczewski J, Polanski Z, et al. Restricted myogenic potential of mesenchymal stromal cells isolated from umbilical cord. Cell Transplant. 2012; 21(8):1711–26. [PubMed: 22525423]
29. Vieira NM, Zucconi E, Bueno CR Jr. Secco M, Suzuki MF, Bartolini P, et al. Human multipotent mesenchymal stromal cells from distinct sources show different *in vivo* potential to differentiate into muscle cells when injected in dystrophic mice. Stem Cell Rev. 2010; 6(4):560–6. [PubMed: 20821076]
30. Asumda FZ, Chase PB. Age related changes in rat bone-marrow mesenchymal stem cell plasticity. BMC Cell Biol. 2011; 12:44. [PubMed: 21992089]
31. Guan J, Wang F, Li Z, Chen J, Guo X, Liao J, et al. The stimulation of the cardiac differentiation of mesenchymal stem cells in tissue constructs that mimic myocardium structure and biomechanics. Biomater. 2011; 32(24):5568–80.
32. Lopez Y, Lutjemeier B, Seshareddy K, Trevino E, Hageman K, Musch T, et al. Wharton's jelly or bone marrow mesenchymal stromal cells improve cardiac function following myocardial infarction for more than 32 weeks in a rat model: A preliminary report. Curr Stem Cell Res Ther. 2013; 8(1):46–59. [PubMed: 23270633]
33. Mistry, S.; Anthony, JK.; Harris, IR.; Harmon, AM.; Messina, DJ.; Seyda, S.; Yi, C.; Gosiewska, AA. Postpartum cells derived from umbilical cord tissue, and methods of making and using the same.. 2010. US20100210013
34. Vitelli, FP.; Wolf, DA.; Rudd, D. Cell composition for tissue regeneration.. 2009. US20090068153
35. Liao J, Hammerick KE, Challen GA, Goodell MA, Kasper FK, Mikos AG. Investigating the role of hematopoietic stem and progenitor cells in regulating the osteogenic differentiation of mesenchymal stem cells *in vitro*. J Orthop Res. 2011; 29(10):1544–53. [PubMed: 21495066]
36. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. Cytotherapy. 2006; 8(4):315–7. [PubMed: 16923606]
37. Asumda FZ, Chase PB. Age related changes in rat bone-marrow mesenchymal stem cell plasticity. BMC Cell Biol. 2011; 12:44. [PubMed: 21992089]
38. Wu KH, Zhou B, Yu CT, Cui B, Lu SH, Han ZC, et al. Therapeutic potential of human umbilical cord derived stem cells in a rat myocardial infarction model. Ann Thorac Surg. 2007; 83(4):1491–8. [PubMed: 17383364]
39. Yoon J, Min BG, Kim YH, Shim WJ, Ro YM, Lim DS. Differentiation, engraftment and functional effects of pretreated mesenchymal stem cells in a rat myocardial infarct model. Acta Cardiol. 2005; 60(3):277–84. [PubMed: 15999467]
40. Zhang H, Fazel S, Tian H, Mickle DA, Weisel RD, Fujii T, et al. Increasing donor age adversely impacts beneficial effects of bone marrow but not smooth muscle myocardial cell therapy. Am J Physiol Heart Circ Physiol. 2005; 289(5):H2089–H96. [PubMed: 16219813]
41. Shi D, Reinecke H, Murry CE, Torok-Storb B. Myogenic fusion of human bone marrow stromal cells, but not hematopoietic cells. Blood. 2004; 104(1):290–4. [PubMed: 15010375]
42. Kunisaki Y, Frenette PS. The secrets of the bone marrow niche: Enigmatic niche brings challenge for HSC expansion. Nat Med. 2012; 18(6):864–5. [PubMed: 22673997]
43. Mendez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, Lira SA, et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature. 2010; 466(7308):829–34. [PubMed: 20703299]
44. Bakhshi T, Zabriskie RC, Bodie S, Kidd S, Ramin S, Paganessi LA, et al. Mesenchymal stem cells from the Wharton's jelly of umbilical cord segments provide stromal support for the maintenance

of cord blood hematopoietic stem cells during long term *ex vivo* culture. Transfusion. 2008; 48(12):2638–44. [PubMed: 18798803]

45. Devine SM, Hoffman R. Role of mesenchymal stem cells in hematopoietic stem cell transplantation. Curr Opin Hematol. 2000; 7(6):358–63. [PubMed: 11055509]
46. Hao L, Sun H, Wang J, Wang T, Wang M, Zou Z. Mesenchymal stromal cells for cell therapy: Besides supporting hematopoiesis. Int J Hematol. 2012; 95(1):34–46. [PubMed: 22183780]
47. Horwitz EM, Maziarz RT, Kebriaei P. MSCs in hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011; 17(1 Suppl):S21–S9. [PubMed: 21195306]
48. Jang YK, Jung DH, Jung MH, Kim DH, Yoo KH, Sung KW, et al. Mesenchymal stem cells feeder layer from human umbilical cord blood for *ex vivo* expanded growth and proliferation of hematopoietic progenitor cells. Ann Hematol. 2006; 85(4):212–25. [PubMed: 16391912]
49. Lazarus HM, Koc ON, Devine SM, Curtin P, Maziarz RT, Holland HK, et al. Cotransplantation of HLA-identical sibling culture expanded mesenchymal stem cells and hematopoietic stem cells in hematologic malignancy patients. Biol Blood Marrow Transplant. 2005; 11(5):389–98. [PubMed: 15846293]
50. Pontikoglou C, Deschaseaux F, Sensebe L, Papadaki HA. Bone marrow mesenchymal stem cells: Biological properties and their role in hematopoiesis and hematopoietic stem cell transplantation. Stem Cell Rev. 2011; 7(3):569–89. [PubMed: 21249477]
51. Duffy MM, Ritter T, Ceredig R, Griffin MD. Mesenchymal stem cell effects on T cell effector pathways. Stem Cell Res Ther. 2011; 2(4):34. [PubMed: 21861858]
52. Ennis J, Gotherstrom C, Le BK, Davies JE. *In vitro* immunologic properties of human umbilical cord perivascular cells. Cytotherapy. 2008; 10(2):174–81. [PubMed: 18368596]
53. Fibbe WE, Nauta AJ, Roelofs H. Modulation of immune responses by mesenchymal stem cells. Ann NY Acad Sci. 2007; 1106:272–8. [PubMed: 17442776]
54. Gebler A, Zabel O, Seliger B. The immunomodulatory capacity of mesenchymal stem cells. Trends Mol Med. 2012; 18(2):128–34. [PubMed: 22118960]
55. Kaplan JM, Youd ME, Lodie TA. Immunomodulatory activity of mesenchymal stem cells. Curr Stem Cell Res Ther. 2011; 6(4):297–316. [PubMed: 21190531]
56. Le BK. Immunomodulatory effects of fetal and adult mesenchymal stem cells. Cytotherapy. 2003; 5(6):485–9. [PubMed: 14660044]
57. Le Blanc K, Ringden O. Immunomodulation by mesenchymal stem cells and clinical experience. J Intern Med. 2007; 262(5):509–25. [PubMed: 17949362]
58. Nasef A, Ashammakhi N, Fouillard L. Immunomodulatory effect of mesenchymal stromal cells: Possible mechanisms. Regen Med. 2008; 3(4):531–46. [PubMed: 18588475]
59. Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. Blood. 2007; 110(10):3499–506. [PubMed: 17664353]
60. Prockop DJ, Oh JY. Mesenchymal stem/stromal cells (MSCs): Role as guardians of inflammation. Mol Ther. 2012; 20(1):14–20. [PubMed: 22008910]
61. Reddy BY, Xu DS, Hantash BM. Mesenchymal stem cells as immunomodulator therapies for immune mediated systemic dermatoses. Stem Cells Dev. 2012; 21(3):352–62. [PubMed: 21864110]
62. Samuelsson H, Ringden O, Lonnies H, Le BK. Optimizing *in vitro* conditions for immunomodulation and expansion of mesenchymal stromal cells. Cytotherapy. 2009; 11(2):129–36. [PubMed: 19152151]
63. Weiss ML, Anderson C, Medicetty S, Seshareddy KB, Weiss RJ, VanderWerff I, et al. Immune properties of human umbilical cord Wharton's jelly derived cells. Stem Cells. 2008; 26(11):2865–74. [PubMed: 18703664]
64. Yagi H, Soto-Gutierrez A, Parekkadan B, Kitagawa Y, Tompkins RG, Kobayashi N, et al. Mesenchymal stem cells: Mechanisms of immunomodulation and homing. Cell Transplant. 2010; 19(6):667–79. [PubMed: 20525442]
65. Yi T, Song SU. Immunomodulatory properties of mesenchymal stem cells and their therapeutic applications. Arch Pharm Res. 2012; 35(2):213–21. [PubMed: 22370776]

66. Cho PS, Messina DJ, Hirsh EL, Chi N, Goldman SN, Lo DP, et al. Immunogenicity of umbilical cord tissue derived cells. Blood. 2008; 111(1):430–8. [PubMed: 17909081]
67. Polchert D, Sobinsky J, Douglas G, Kidd M, Moadsiri A, Reina E, et al. IFN-gamma activation of mesenchymal stem cells for treatment and prevention of graft versus host disease. Eur J Immunol. 2008; 38(6):1745–55. [PubMed: 18493986]
68. Najar M, Rouas R, Raicevic G, Boufker HI, Lewalle P, Meuleman N, et al. Mesenchymal stromal cells promote or suppress the proliferation of T lymphocytes from cord blood and peripheral blood: The importance of low cell ratio and role of interleukin-6. Cytotherapy. 2009; 11(5):570–83. [PubMed: 19565371]
69. Shi M, Liu ZW, Wang FS. Immunomodulatory properties and therapeutic application of mesenchymal stem cells. Clin Exp Immunol. 2011; 164(1):1–8. [PubMed: 21352202]
70. Soleymaninejadian E, Pramanik K, Samadian E. Immunomodulatory properties of mesenchymal stem cells: cytokines and factors. Am J Reprod Immunol. 2012; 67(1):1–8. [PubMed: 21951555]
71. Sotiropoulou PA, Papamichail M. Immune properties of mesenchymal stem cells. Methods Mol Biol. 2007; 407:225–43. [PubMed: 18453259]
72. Tyndall A, Walker UA, Cope A, Dazzi F, De BC, Fibbe W, et al. Immunomodulatory properties of mesenchymal stem cells: A review based on an interdisciplinary meeting held at the kennedy institute of rheumatology division, London, UK, 31 October 2005. Arthritis Res Ther. 2007; 9(1): 301. [PubMed: 17284303]
73. Uccelli A, Moretta L, Pistoia V. Immunoregulatory function of mesenchymal stem cells. Eur J Immunol. 2006; 36(10):2566–73. [PubMed: 17013987]
74. English K, Barry FP, Field-Corbett CP, Mahon BP. IFN-gamma and TNF-alpha differentially regulate immunomodulation by murine mesenchymal stem cells. Immunol Lett. 2007; 110(2):91–100. [PubMed: 17507101]
75. Ryan JM, Barry F, Murphy JM, Mahon BP. Interferon-gamma does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells. Clin Exp Immunol. 2007; 149(2):353–63. [PubMed: 17521318]
76. Stagg J, Pommey S, Eliopoulos N, Galipeau J. Interferon-gamma-stimulated marrow stromal cells: A new type of nonhematopoietic antigen-presenting cell. Blood. 2006; 107(6):2570–7. [PubMed: 16293599]
77. Heidaran, M.; Wang, JL.; Ye, Q.; Zeitlin, A.; Dulaney, CS. Co-culture of placental stem cells and stem cells from a second source.. 2010. 2013. US7700090 US8455250
78. Emerson, SG.; Clarke, MF.; Palsson, BO. Method for the *ex vivo* replication of stem cells, for the optimization of hematopoietic progenitor cell cultures, and for increasing the metabolism, GMCSF secretion and/or IL-6 secretion of human stromal cells.. 1995. US5437994
79. Emerson, SG.; Clarke, MF.; Palsson, BO. Methods, compositions and devices for growing human hematopoietic cells.. 1997. US5605822
80. Torok-Storb, B.; Roecklein, BA.; Johnson, G. Human marrow stromal cell lines which sustain hematopoieses.. 1999. US5879940
81. Merchav, S.; Meretski, S. Method of expanding undifferentiated hemopoietic stem cells.. 2009. US7534609
82. Merchav, S.; Meretski, S.; Zipori, D.; Kadouri, A. Method of preparing a conditioned medium from a confluent stromal cell culture.. 2010. US7678573
83. Haynesworth, SE.; Caplan, AI.; Gerson, SL.; Lazarus, HM. Enhancing bone marrow engraftment using MSCS.. 1998. US5733542
84. Caplan, AI.; Haynesworth, SE.; Gerson, SL.; Lazarus, HM. Enhancing hematopoietic progenitor cell engraftment using mesenchymal stem cells.. 2000. US6010696
85. Paludan, C.; Edinger, J.; Harbacheuski, R.; Murray, R.; Hariri, RJ. Immunomodulation using placental stem cells.. 2010. US7682803
86. Paludan, C.; Edinger, J.; Harbacheuski, R.; Murray, R.; Hariri, RJ. Treatment of multiple sclerosis using placental stem cells.. 2012. US8216566
87. Ichim, TE. Stem cell mediated treg activation/expansion for therapeutic immune modulation.. 2012. US8241621

88. Bhatia, M.; Madrenas, J.; Ferber, IA.; Majumdar, AS. Using undifferentiated embryonic stem cells to control the immune system.. 2010. US7799324

89. McIntosh, K.; Klyushnenkova, E. Method of preparing suppressor T cells with allogeneic mesenchymal stem cells.. 2001. US6281012

90. McIntosh, KR.; Mosca, JD.; Klyushnenkova, E. Mesenchymal stem cells for prevention and treatment of immune responses in transplantation.. 2005. US6328960

91. Bruder, SP.; McIntosh, KR.; Marshak, DR.; Mosca, JD. Uses for non-autologous mesenchymal stem cells.. 2002. US6355239

92. McIntosh, KR.; Mosca, JD.; Klyushnenkova, E. Mesenchymal stem cells for prevention and treatment of immune responses in transplantation.. 2002. US6368636

93. Mcintosh, K.; Klyushnenkova, E. Suppressor cells induced by culture with mesenchymal stem cells for treatment of immune responses in transplantation.. 2004. US6685936

94. Mosca, JD.; Mcintosh, KR. Mesenchymal stem cells as immunosuppressants.. 2004. US6797269

95. Bruder, SP.; McIntosh, KR.; Marshak, DR.; Mosca, JD. Uses for non-autologous mesenchymal stem cells.. 2006. US7029666

96. Kotobuki N, Katsube Y, Katou Y, Tadokoro M, Hirose M, Ohgushi H. *In vivo* survival and osteogenic differentiation of allogeneic rat bone marrow mesenchymal stem cells (MSCs). Cell Transplant. 2008; 17(6):705–12. [PubMed: 18819258]

97. Francois M, Galipeau J. New insights on translational development of mesenchymal stromal cells for suppressor therapy. J Cell Physiol. 2012; 227(11):3535–8. [PubMed: 22378308]

98. Liu S, Yuan M, Hou K, Zhang L, Zheng X, Zhao B, et al. Immune characterization of mesenchymal stem cells in human umbilical cord Wharton's jelly and derived cartilage cells. Cell Immunol. 2012; 278(1-2):35–44. [PubMed: 23121974]

99. Niemeyer P, Kornacker M, Mehlhorn A, Seckinger A, Vohrer J, Schmal H, et al. Comparison of immunological properties of bone marrow stromal cells and adipose tissue-derived stem cells before and after osteogenic differentiation *in vitro*. Tissue Eng. 2007; 13(1):111–21. [PubMed: 17518585]

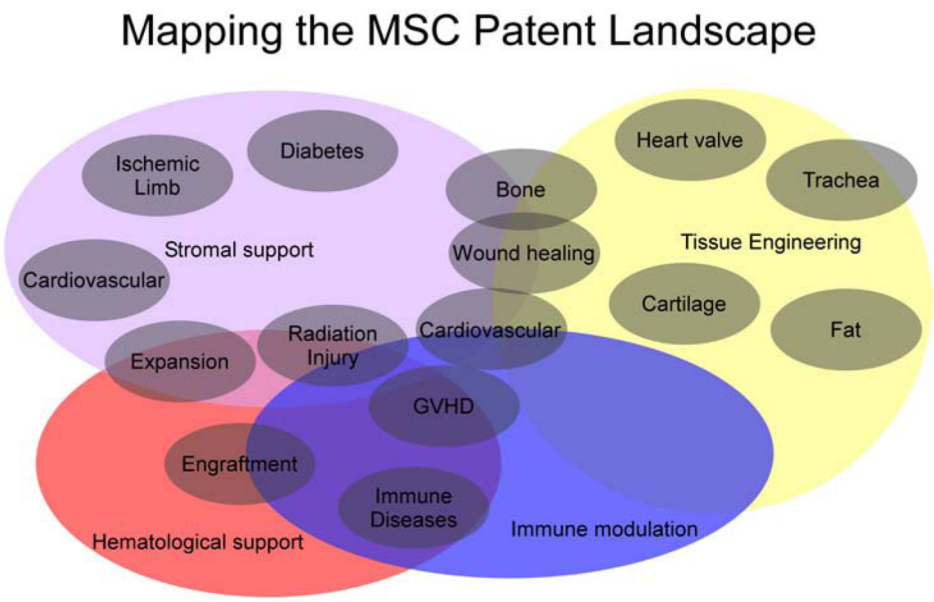

Fig. (1). Mapping the patent landscape

The clinical application and the patent landscape are based upon the physiology of mesenchymal stromal cells (MSCs). Here, MSC physiology is parsed into stromal support, tissue engineering, immune modulation or hematological support. Within each region, potential applications or uses of MSCs are identified. For example, as shown in the tissue engineering zone, based upon MSC's ability to differentiate into tissues of mesenchymal lineages, they have been used to construct artificial heart valves, trachea or assist with wound healing. As shown in the immune modulation zone, the immune modulation properties of MSCs have been leveraged in the clinic for treatment of graft versus host disease (GVHD) and other immune diseases. In the hematological support zone, MSCs in the bone marrow have the ability to support hematopoietic stem cells within the niche. This physiological function has been leveraged to co-graft MSCs during hematological stem cell transplantation, or to assist with ex vivo expansion of blood forming stem cells prior to transplantation. Additionally, MSCs given following radiation injury can assist with hematological recovery. In the stromal support zone, the role of MSCs to provide stromal support has been leveraged via regenerative medicine applications such as support of ischemic limb, diabetes, radiation injury, wound healing, etc. Note that the physiological of MSCs does not cleanly partition and they have areas of overlap.

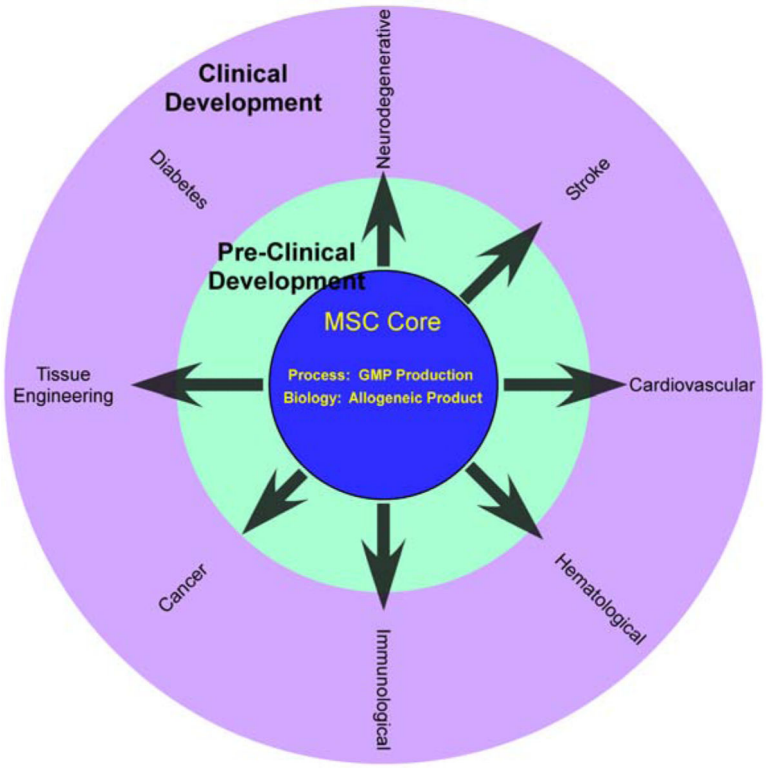

Fig. (2). Taking mesenchymal stromal cells (MSCs) from the laboratory into clinical trial

Once clinical applications have been identified based upon cell physiology, a three stage process is needed to move from laboratory bench into clinical trial. As shown in the blue core, the first step is to produce a reliable standardized process that can produce a large number of cells suitable for clinical use. This requires generating cells using good manufacturing process (GMP). This GMP process should be scaled up to produce a large batch of cells which will be tested for their value as an allogeneic product (as to leverage both economies of scale and a simplified validation process). In some applications, MHC tissue matching may be needed or an allogeneic product may be unsuitable due to scavenging by the host immune system. This may result in loss of persistence, or prevent true engraftment. If this is the case, MSCs will need to be prepared as one-offs (single, patient specific batches) and the costs of manufacture and validation are higher. Once the standard operating procedures are established and the GMP cells are prepared, they are tested for clinical use through using pre-clinical animal testing of the disease. An attempt is made to model as closely as possible the way that the MSCs will be used in human patients. Pre-clinical testing is used to validate the efficacy of the GMP cells, to evaluate mechanism(s) of MSC action, their biodistribution and toxicity and their persistence following transplantation. Pre-clinical testing is the final step leading to testing in humans. The Federal Drug Administration (FDA) can provide guidance, and a meeting with the FDA during the early phases of translation may clarify the GMP requirements and the pre-clinical testing requirements. In this figure, the arrows indicate clinical indications that have moved from the laboratory bench into clinical trial for MSCs.

Table 1

Summary of Issued US Patents Relevant to the Application of MSCs Including UCMSCs in Hematopoiesis, Immune Modulation, and Musculoskeletal Regeneration.

Table 1 US Patent ISSUED					
Physiology	**MSC source**	**US Patent**	**Granted date**	**Title**	**Assignee**
Stromal Support	Bone marrow	5437994	1-Aug-95	Method for the *ex vivo* replication of stem cells, for the optimization of hematopoietic progenitor cell cultures, and for increasing the metabolism, GM-CSF secretion and/or IL-6 secretion of human stromal cells	Regents of the University of Michigan
	Bone marrow	5605822	25-Feb-97	Methods, compositions and devices for growing human hematopoietic cells	Regents of the University of Michigan
	Bone marrow	5733542	31-Mar-98	Enhancing bone marrow engraftment using MSCS	
	Bone marrow	5804446	8-Sep-98	Blood-borne mesenchymal cells	Cytokine Pharmasciences, Inc.
	Bone marrow	5879940	9-Mar-99	Human marrow stromal cell lines which sustain hematopoieses	Fred Hutchinson Cancer Research Center
	Bone marrow	6010696	4-Jan-00	Enhancing hematopoietic progenitor cell engraftment using mesenchymal stem cells	Osiris
	Bone marrow	6054121	25-Apr-00	Modulation of immune responses in blood-borne mesenchymal cells	Cytokine Pharmasciences, Inc.
	Bone marrow	6103522	15-Aug-00	Human marrow stromal cell lines which sustain hematopoiesis	Fred Hutchinson Cancer Research Center
	Bone marrow	7129086	31-Oct-06	Human marrow stromal cell lines which sustain hematopoiesis	Fred Hutchinson Cancer Research Center
	Bone marrow	7534609	19-May-09	Method of expanding undifferentiated hemopoietic stem cells	Pluristem Life Systems Inc.
	Bone marrow	7678573	16-Mar-10	Method of preparing a conditioned medium from a confluent stromal cell culture	Pluristem Life Systems Inc.
	Placenta	7700090	20-Apr-10	Co-culture of placental stem cells and stem cells from a second source	Anthrogenesis Corporation
Immune Modulation	Bone marrow	6281012	28-Aug-01	Method of preparing suppressor T cells with allogeneic mesenchymal stem cells	Osiris
	Bone marrow	6328960	11-Dec-01	Mesenchymal stem cells for prevention and treatment of immune responses in transplantation	Osiris
	Bone marrow	6355239	12-Mar-02	Uses for non-autologous mesenchymal stem cells	Osiris
	Bone marrow	6368636	9-Apr-02	Mesenchymal stem cells for prevention and treatment of immune responses in transplantation	Osiris

Table 1 US Patent ISSUED

Physiology	MSC source	US Patent	Granted date	Title	Assignee
	Bone marrow	6685936	3-Feb-04	Suppressor cells induced by culture with mesenchymal stem cells for treatment of immune responses in transplantation	Osiris
	Bone marrow	6797269	28-Sep-04	Mesenchymal stem cells as immunosuppressants	Osiris
	Bone marrow	6875430	5-Apr-05	Mesenchymal stem cells for prevention and treatment of immune responses in transplantation	Osiris
	Bone marrow	7029666	18-Apr-06	Uses for non-autologous mesenchymal stem cells	Osiris
	Bone marrow	7442390	28-Oct-08	Method for enhancing engraftment of cells using mesenchymal progenitor cells	University of South Florida
	Placenta	7682803	23-Mar-10	Immunomodulation using placental stem cells	Anthrogenesis Corporation
	Bone marrow	7691415	6-Apr-10	Method for preventing, or reducing the severity of, graft-versus-host disease using pluri-differentiated mesenchymal progenitor cells	University of South Florida
	Bone marrow	7691415	6-Apr-10	Method for preventing, or reducing the severity of, graft-versus-host disease using pluri-differentiated mesenchymal progenitor cells	University of South Florida
	ESC	7799324	21-Sep-10	Using undifferentiated embryonic stem cells to control the immune system	Geron
	Bone marrow	8057826	15-Nov-11	Method for preventing, or reducing the severity of, graft-versus-host disease using pluri-differentiated mesenchymal progenitor cells	University of South Florida
	MAPC/ bone marrow	8147824	3-Apr-12	Immunomodulatory properties of multipotent adult progenitor cells and uses thereof	Athersys, Inc., Oregon Health and Science University
	Placenta	8216566	10-Jul-12	Treatment of multiple sclerosis using placental stem cells	Anthrogenesis Corporation
	Bone marrow	8221741	17-Jul-12	Methods for modulating inflammatory and/or immune responses	
	Adipose	8241621	14-Aug-12	Stem cell mediated treg activation/expansion for therapeutic immune modulation	Medistem Laboratories
Musculoskeletal Regeneration	Umblical cord	5919702	6-Jul-99	Production of cartilage tissue using cells isolated from Wharton's jelly	Advanced Tissue Science, Inc.
	Umblical cord	5962325	5-Oct-99	Three-dimensional stromal tissue cultures	Advanced Tissue Science, Inc.

Table 2

Summary of Filed US Patents Relevant to the Application of MSCs Including Ucmscs in Hematopoiesis, Immune Modulation, and Musculoskeletal Regeneration.

Table 2 US Patent APPLICATIONS				
Source	**US Patent**	**Filed date**	**Title**	**Assignee**
Bone marrow	2003/0203483	3-Oct-02	Human mesenchymal progenitor cell	
Bone marrow	2003/0003084	2-Jan-03	Human mesenchymal progenitor cell	
MAPC/ bone marrow	2004/0107453	5-Jan-04	Multipotent adult stem cells, sources thereof, methods of obtaining same, methods of differentiation thereof, methods of use thereof and cells derived thereof	
ESC	2004/0208857	22-Jan-04	Use of cells derived from embryonic stem cells for increasing transplantation tolerance and for repairing damaged tissue	
Bone marrow	2005/0059147	9-Jul-04	Human mesenchymal progenitor cell	
Adipose	2007/0122393	14-Jul-06	Immunophenotype and immunogenicity of human adipose derived cells	
MAPC/ bone marrow	2009/0104163	9-Nov-06	Immunomodulatory properties of multipotent adult progenitor cells and uses thereof	Athersys, Inc., Oregon Health and Science University
Umblical cord	2009/0285842	4-May-07	Immune privileged and modulatory progenitor cells	
Bone marrow	2010/0111905	8-Nov-07	Methods for improved engraftment following stem cell transplantation	Aldagen, Inc.
Placenta	2008/0226595	12-Feb-08	Treatment of inflammatory diseases using placental stem cells	
Bone marrow	2008/0254007	19-May-08	Human mesenchymal progenitor cell	
Oral mucosa	2011/0110900	11-Jun-09	Novel adult progenitor cell	
Multiple sources	2012/0121611	28-Jul-11	Method of treating autoimmune disease with mesenchymal stem cells	Tissue Regeneration Therapeutics, Inc.
Umblical cord	2009/0269318	11-Jun-09	Progenitor cells from Wharton's jelly of human umbilical cord	Ethicon, Incorporated
Umblical cord	US2010/0210013	19-Feb-09	A. Postpartum cells derived from umbilical cord tissue, and methods of making and using the same	
Umblical cord	2009/0068153	6-Sep-07	Cell composition for tissue regeneration	

Table 3

Summary of Filed International Patents Relevant to the Application of MSCs Including Ucmscs in Hematopoiesis, Immune Modulation, and Musculoskeletal Regeneration.

Table 3 International Patent APPLICATIONS				
Source	**Patent**	**Filed date**	**Title**	**Assignee**
Umblical cord	7128115 PCT/CA07/000781	4-May-07	Immune privileged and modulatory progenitor cells	
Adipose	8036374 PCT/US07/020415	20-Sep-07	Allogeneic stem cell transplants in non-conditioned recipients	Medistem Laboratories, Inc
Bone marrow	2089042 PCT#US2007#084037	8-Nov-07	Methods for improved engraftment following stem cell transplantation	Aldagen, Inc.
Bone marrow	08097828 PCT/US08/052759	1-Feb-08	Method for isolating mesenchymal stromal cells	
Adipose	10063743 PCT/EP09/066198	3-Dec-08	Methods for the preparation of adipose derived stem cells and utilizing said cells in the treatment of diseases	Cellerix, S.A.
Bone marrow	2296674 PCT#GB2009#001443	11-Jun-09	Novel adult progenitor cell	
Gingiva	10090843 PCT/US10/021531	20-Jan-10	Gingiva derived stem cell and its application in immunomodulation and reconstruction	University of Southern California
Omentum	201108 PCT/US10/028577	25-Mar-10	Omentum as a source of stromal/stem cells and medical treatments using omentum stromal/stem cells	
Adipose	11047345 PCT/US10/052953	15-Oct-10	Methods of treating diseases of conditions using mesenchymal stem cells	
Bone marrow	2496711 PCT#SG2010#000422	2-Nov-10	Methods for monitoring cellular states and for immortalizing mesenchymal stem cells	
ESCs	11054100 PCT/CA10/001771	5-Nov-10	Stem cell extracts and uses thereof for immune modulation	
Amnion	12083021 PCT/US11/065158	15-Dec-11	Treatment of immune-related diseases and disorders using amnion derived adherent cells	Anthrogenesis Corporation
Bone marrow	201227 PCT/EP11/074232	29-Dec-11	Protection from lethal irradiation with mesenchymal stromal cells	